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30 September 2005

Science

Vol. 309 No. 5744
Pages 2121–2296 $10

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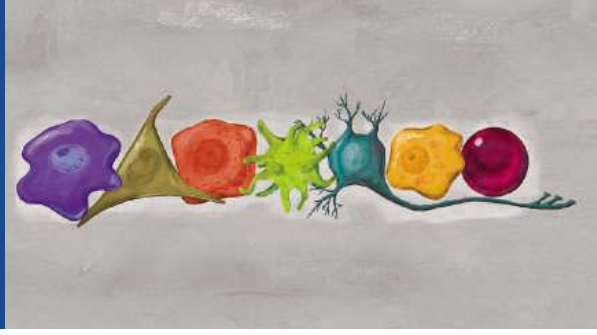

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- **rat Pentraxin 2/SAP**
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- **rat Robo1**
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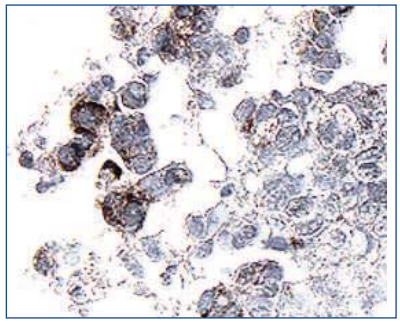
- **mouse Wnt-8a**



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Science

COVER A male North American barn swallow (*Hirundo rustica erythrogaster*) displaying his ventral coloration. Males whose feathers are experimentally darkened during the breeding season receive relatively greater reproductive benefits from their mates than in previous breeding attempts, indicating that these color signals are used for continual assessment of mate quality. See page 2210. [Image: Marie Read]

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30 September 2005
Number 5744

DEPARTMENTS

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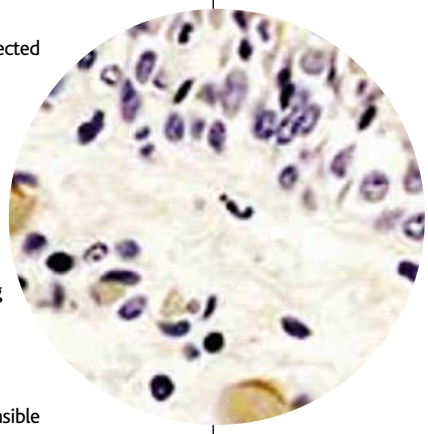

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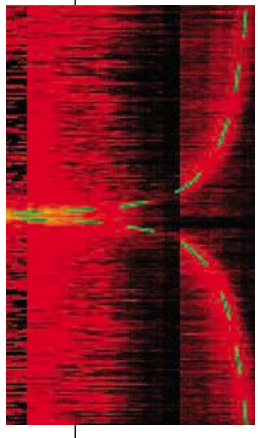
RESEARCH ARTICLES



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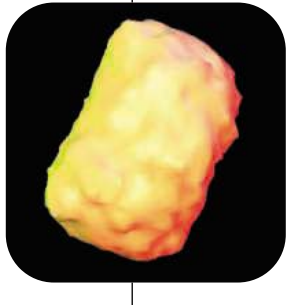
REPORTS



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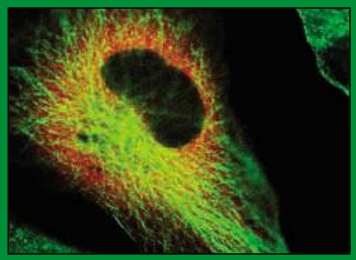

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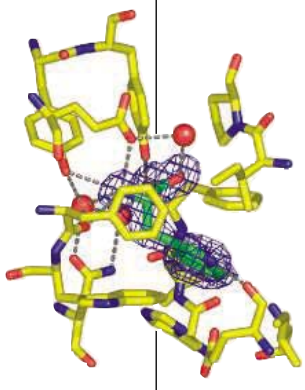
Reports continued



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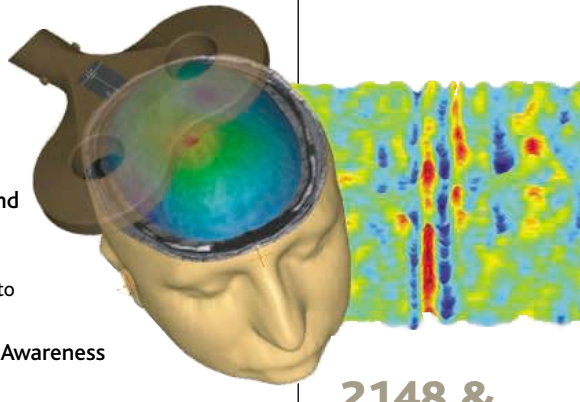

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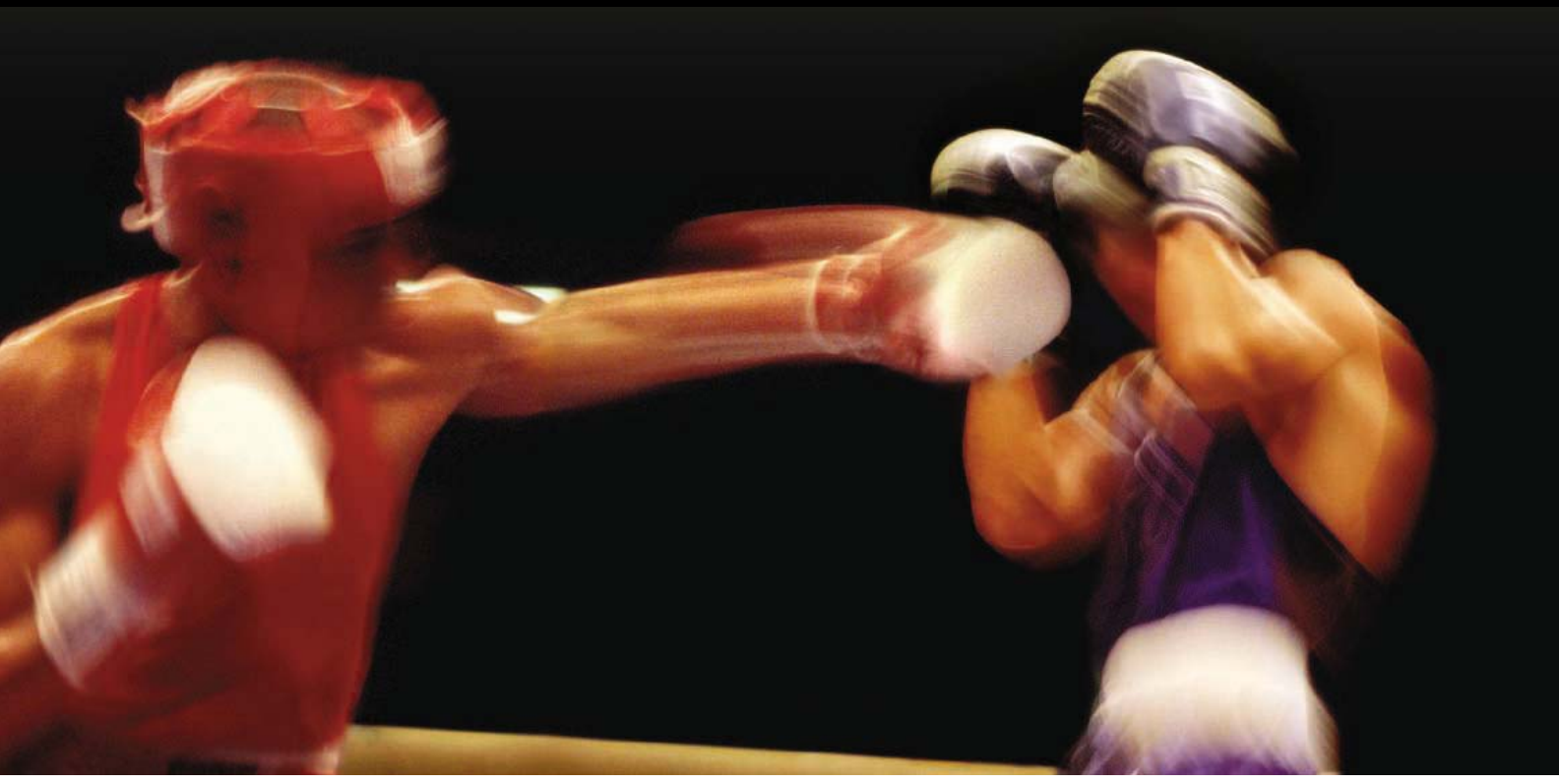

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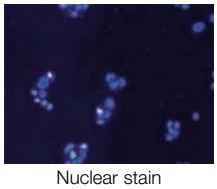
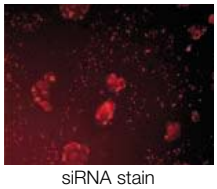


Nuclear stain



siRNA stain

Delivery of siRNA in MCF-7 cells. Cells were transfected with 10 nM siGLO siRNA using 0.5 µl siLentFect. After 24 hr, cells were imaged to show nuclear staining by Hoechst 33342 dye (top) or the location of fluorescent siRNA (bottom).

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Researchers restore hair to bald mice, but men may have to wait.

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Keeping the Leap
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Summer research leads to grad school.

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US: Powered by Nature *A. Fazekas*
Sean Shaheen shares his story about his work with organic photovoltaic cells.

US: A Year with a Twist *G. Muir*
Gary Muir reflects on his first year as a faculty member at a small college.

MiSciNet: Summer Breakthroughs in Science—An Educational Journey *E. Francisco*
Imran Babar says his summer research experiences influenced him to pursue graduate school.

GrantsNet: International Grants and Fellowships Index *Next Wave Staff*
Get the latest listing of funding opportunities in Europe, Asia, and the Americas.

Web Log: European Science Careers News Clips *E. Pain and A. Forde*
Students in Spain get research money and a conference discusses the new European charter for researchers.

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Read up on a new report on research institution policies on tenure and family support.

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Perspective: From Bedside to Bench—Research in Comorbidity and Aging *G. D. Wieland*
Conference discusses the challenge of treating multiple overlapping health problems in the elderly.

News Focus: Appetite Suppressant *M. Leslie*
Suicide-squelching molecule also slows cellular cannibalism.

News Focus: Battle of the Sexes *R. J. Davenport*
Male bean weevils shape female aging.

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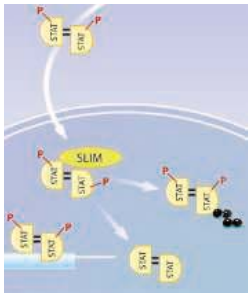

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Perspective: Intracellular Glucocorticoid Signaling—A Formerly Simple System Turns Stochastic *G. P. Chrousos and T. Kino*
Numerous glucocorticoid receptor isoforms add a new layer of complexity to glucocorticoid signaling.

Perspective: SLIM Trims STATs—Ubiquitin E3 Ligases Provide Insights for Specificity in Regulation of Cytokine Signaling *D. Ungureanu and O. Silvennoinen*
JAKS and STATs are both targets of ubiquitin-mediated regulation.

Letters: Shaky Ground for Lysosome-Dependent Membrane Repair *R. A. Steinhardt*
This letter comments on an STKE Perspective on mechanisms of membrane resealing.

Letters: Response to Shaky Ground for Lysosome-Dependent Membrane Repair *N. W. Andrews*
This response highlights differences in opinion on the role of lysosomes in plasma membrane resealing.

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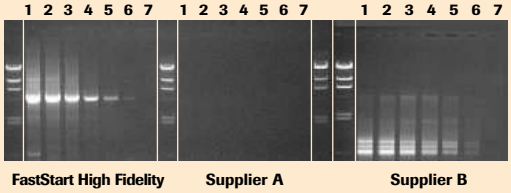

1:100 ng hum. gen. DNA
2: 50 ng hum. gen. DNA
3: 25 ng hum. gen. DNA
4: 10 ng hum. gen. DNA
5: 5 ng hum. gen. DNA
6: 1 ng hum. gen. DNA
7: 0 ng hum. gen. DNA

Figure 1. Amplification of a 4.8 kb tPA fragment from different amounts of human genomic DNA, using conditions recommended by each manufacturer.

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edited by Stella Hurtley and Phil Szuromi

Dynamic Spin Control in Double Quantum Dots

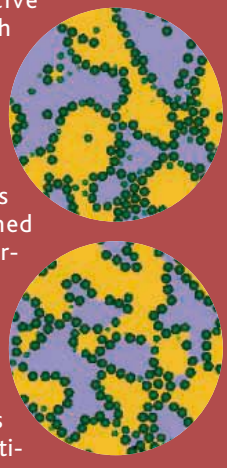
The coupling of electron spins between adjacent quantum dots can form the basis of a quantum logic gate. However, each electron on a dot couples to the large and random background field of about 1 million nuclear spins in the substrate, and these interactions lead to spin-state memory loss and mixing between spin-singlet and spin-triplet states. Recent work has looked at mitigating the spin-state mixing statically by controlling the coupling strength between quantum dots or by polarizing the background nuclear magnetic field. Using fast voltage pulses to control the exchange interaction between the electrons on adjacent dots, **Petta *et al.*** (p. 2180, published online 1 September 2005; see the Perspective by **DiVincenzo**) now show that dynamical coherent control of the spin states can also be achieved, which leads to a substantially increased lifetime of the prepared coupled spin states.

Imaging Spin Transport

"Spintronics" technology will use the spin state of electrons, rather than charge, to represent information, and will require a number of transport properties to be brought together. For example, it would be useful to be able to inject a spin-polarized current electrically with a ferromagnetic source contact, modulate the polarization of the propagating spin current with an electric field, and then detect the spin current with a ferromagnetic drain contact. **Crooker *et al.*** (p. 2191) report magneto-optical Kerr effect images of spin-polarized electrons in a lateral Fe-GaAs-Fe heterostructure, and provide a detailed account of the length scales governing the injection of spin-polarized electrons into the GaAs semiconductor layer.

Jam Session

The demixing of a binary fluid mixture in the presence of colloidal particles was studied by **Stratford *et al.*** (p. 2198; see the Perspective by **Poulin**) through computer simulations. The particles were chosen so that they exhibited neutral wetting with the two liquids and would remained trapped at the interface between the two liquid phases. As coarsening between the fluids proceeded, the interface becomes shorter and the particles became more concentrated and reached a jammed state. This phenomenon can arrest the phase separation and lead to a metastable bicontinuous gel.

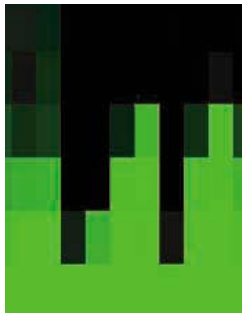


Winding Down

Low-mass stars like the Sun form with their surfaces rotating rapidly, but the rotation slows over time because of magnetic braking and momentum exchange that creates internal velocity gradients. Models of these velocity patterns are in conflict with helioseismology as well as with observations of the element lithium at the stellar surface. **Charbonnel and Talon** (p. 2189) report a model that correctly accounts for both the rotation patterns and lithium abundance in Sun-like stars. The best model incorporates internal gravity waves, much like those responsible for Earth's alternating easterly and westerly zonal winds called the quasi-biennial oscillation.

Mammals, Oxygen, and Oceans

The atmospheric concentration of O_2 has varied considerably during the past 205 million years, rising irregularly from around 10% at the beginning of the Jurassic to 21% today, with a maximum of more than 23% during the Tertiary. How might these changes have affected the evolution of animals? **Falkowski *et al.*** (p. 2202) used their carbon isotopic measurements of carbonates and organic matter, along with published records of sulfur isotopes, to produce a high-resolution reconstruction of atmospheric O_2 concentration since the early Jurassic. They find that O_2 levels approximately doubled over the course of their record, in association with enhanced burial of organic matter on continental shelves resulting from the formation of passive continental margins during the opening of the Atlantic Ocean. There were relatively fast changes in the Jurassic and since the start of the Eocene. The authors suggest that the rise of O_2 levels was a key factor in the evolution, radiation, and the increase in average size of placental mammals since the mid-Cretaceous.



Instant Gratification

The molecular chaperone Hsp90 allows various organisms to exploit existing genetic variation depending upon the prevailing environmental conditions. **Cowen and Lindquist** (p. 2185; see the Perspective by **Heitman**) establish a new role for Hsp90 in the evolution of adaptive traits. In fungal species separated by ~1 billion years of evolution, Hsp90 potentiates the evolution of drug resistance by enabling immediate phenotypic consequences from new mutations. Increased temperature can abolish fungal drug resistance, which provides an explicit mechanism by which fever might be beneficial to the host. In fungal pathogens that are already recalcitrant to antifungal therapy, inhibiting Hsp90 improves response to treatment and, if given in the initial stages of therapy, may impede the de novo evolution of drug resistance.

Keeping Up Appearances

Despite the hundreds of studies of mating systems in socially monogamous vertebrates, little is known about the decision rules that drive females' allocation of paternity to their social, versus extra-pair, mates. These decision rules underlie the control and function of the variable reproductive strategies that are prevalent in nature. In a field population of barn swallows (*Hirundo rustica*), **Safran *et al.*** (p. 2210) analyzed genetic measures of paternity before and after a known signal of male quality (plumage coloration)

CONTINUED ON PAGE 2135

CREDITS (TOP TO BOTTOM): STRATFORD *ET AL.*; COWEN *ET AL.*

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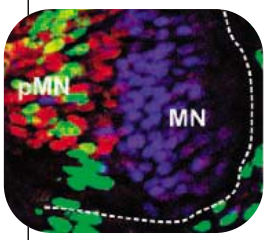
was manipulated. The females shift paternity to more colorful males, which suggests the presence of continual, flexible decision rules for paternity allocation. Thus, it is important for male birds to maintain their signals of quality even after they form a pair bond.



CREDIT: RAO ET AL.

Retinoic Acid Responder

Retinoic acid causes changes in gene expression that are essential for development of spinal motor neurons in the chick. **Rao and Sockanathan** (p. 2212) now find that glycerophosphodiester phosphodiesterase 2 (GDE2) shows increased expression in response to retinoic acid. In developing embryos, GDE2 was necessary and sufficient to promote differentiation of motor neurons.

Rev1 Rescues Replication

To maintain the fidelity of stored DNA codes, DNA polymerases use the complementarity of the nucleotide bases to ensure the correct incorporation of the incoming base against the template base: A with T, G with C, and so forth. **Nair *et al.*** (p. 2219) now show that unlike other polymerases, the highly specialized Y family polymerase Rev1 does not use the complementarity of the template G to incorporate the incoming C. Rather, the protein itself specifies the identity of the incoming base: Both the template G and incoming C are bound to the protein, and not to each other. In this way, Rev1 can replicate through damaged G residues that would otherwise stop the processing of replicative polymerases. Thus, Rev1 can rescue the genome from further potentially lethal damage.

Keeping Options Open

The brain's visual cortex is normally constructed to balance inputs from both eyes. When input is unbalanced during an early critical period, such as when vision from one eye is blocked, the visual cortex adjusts accordingly. However, the critical period is finite. Beyond this time of juvenile flexibility, the cortex cannot readjust to unbalanced visual inputs. **McGee *et al.*** (p. 2222; see the news story by **Miller**) now find that mutations in the Nogo-66 receptor (NgR) can keep the ocular dominance critical period in mice from closing. Closure of the critical period for whisker barrel fields is not affected by NgR mutations, which suggests that there may be more than one mechanism governing the extent of different critical periods.

To Neglect or Not to Neglect...

Unilateral neglect patients usually ignore events in one-half of the world around them. **Thiebaut de Schotten *et al.*** (p. 2226; see the Perspective by **Gaffan**) used intraoperative direct intracranial stimulation to assess the role of cortical and subcortical areas in attentional neglect. Two patients undergoing surgery for tumor resection were subjected to direct electrical stimulation of areas in the parietal and temporal lobes (lesions of which have been implicated in attentional neglect), as well as in an underlying region of subcortical white matter. Stimulation of the supramarginal gyrus and the caudal superior temporal gyrus produced behavior typical for unilateral neglect. The most profound effect was observed during stimulation of an area of underlying white matter that corresponded to the superior occipitofrontal fasciculus that connects the parietal and the frontal cortex.

Restricted Activities of the Sleeping Brain

The departure of consciousness as we experience "the death of each day's life . . ." has puzzled neuroscientists, who have noticed little change in cortical neuron firing rates between quiet wakefulness and non-REM (rapid eye movement) sleep. **Massimini *et al.*** (p. 2228) now can assess whether the directional connections between brain areas might weaken with the onset of sleep. They applied transcranial magnetic stimulation (TMS) to the premotor area and monitored neural activity in the whole brain with electroencephalography. TMS-evoked activity, which spread to distant cortical areas when subjects were awake, remained locally confined after they fell asleep.

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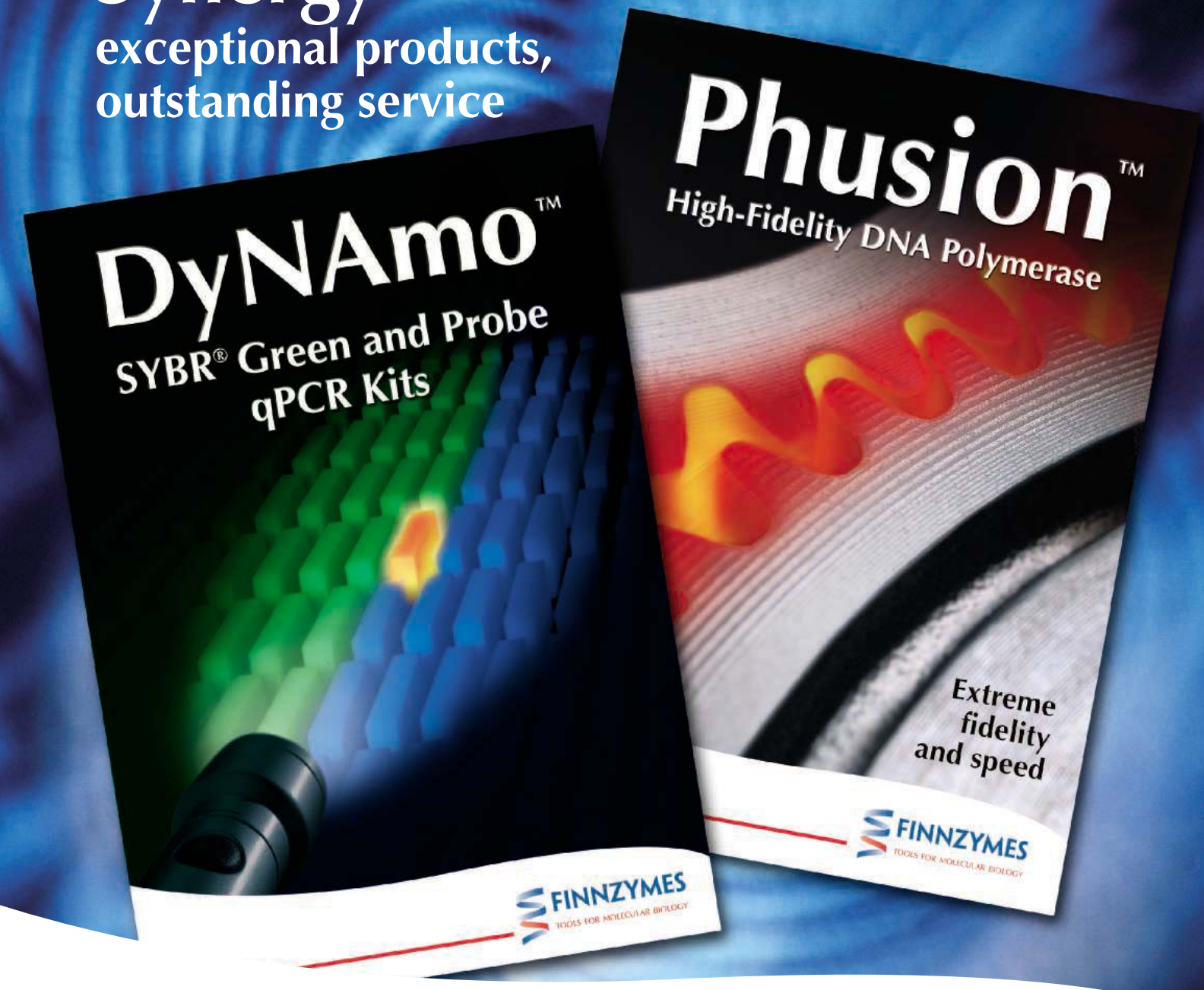

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Risks and Risks

When society makes a decision about some action (to build a dam or approve a new drug, for example), its choice is usually based on a comparison of risks and benefits. If the latter exceed the former, assuming that risks and benefits accrue to the same person or group, the project goes forward. But we do not live in a black-and-white world, and outcomes sometimes don't fall readily into a yes-or-no choice, especially when there are alternative ways of gaining the same benefits. In that case, the only realistic basis for choosing comes down to a comparison of the risks associated with each alternative.

In the United States and some other industrial democracies, where people and their governments tend to be risk-averse, legislatures, courts, and administrative entities usually create a presumption favoring more safety rather than less. The definitions of risk in law are often vague ("reasonable certainty of no harm" or "adequate margin of safety") and are likely to encourage an unrealistic belief that risks can be minimized or even eliminated altogether. A frequent result is that legal choices for administrative agencies or individual decision-makers amount to all-or-none options, leaving little room for intermediates.

But on occasion, a zone opens for risk comparisons, as in the following examples. Suppose a municipality is treating its water supply with chlorination. Chlorine sometimes combines with organic compounds in natural water supplies to form chlorinated hydrocarbons, some of which have carcinogenic potential. The Environmental Protection Agency (EPA) is charged with regulating such substances, but it is also responsible for controlling waterborne infections. In determining appropriate levels of chlorination, the EPA had to balance the risk of such infections against the risk of contamination with small amounts of a potentially cancer-causing substance. In a lengthy negotiation, the EPA undertook a risk-balancing exercise, resulting in a decision about the safe (least risky) level of chlorine addition.

Or suppose you're taking a prescription drug that relieves a painful arthritic condition. Suddenly a study conducted by a large health maintenance organization shows that at doses higher than those used by patients seeking relief from chronic joint pain, there is a risk of cardiac malfunction—a risk twice as great as that of control subjects. You have to decide whether the risk of continuing to take the medicine is greater or less than the risk associated with your mobility loss and pain. Over-the-counter anti-inflammatory drugs may cause some digestive tract problems, so you prefer not to switch to them. There's no history of heart disease in your family, so you become more comfortable with the drug's cardiac risk. In the end, after consultation with your physician, you decide to continue the drug regime despite the warning label.

There may be a lesson here for much larger-scale societal decisions. For a number of reasons, many developed nations have concluded that the risks of nuclear power generation are too great to engage in traditional risk/benefit assessment of its use. But there is a growing scientific consensus that the emission of carbon dioxide and other greenhouse gases, released in the course of energy production and industrial combustion, is related to global warming. It is clear that business as usual will entail increasing climate-associated risks. Nuclear power is an alternative that emits no greenhouse gases. On the other hand, it presents risks that include nuclear accident, diversion and proliferation of fissile material, and uncertainty about the management of high-level waste.

These are substantial risks, all right. But so are those associated with global climate change: rising sea levels, increased frequency of extreme weather events, changes in agricultural productivity, and weather-induced hazards to human health. Balancing these kinds of risks will require complex and difficult decisions, and the need to make them will be a challenge to our societal appetite for no-risk solutions. Just as we compare risks as we seek to protect or improve our personal health, we will need to do so on a larger scale as we seek to manage the environmental effects of our industrial economy. In the latter case, it is pointless to take one option off the table without a serious comparison of risks. We may wish for safe solutions, but neither option is free of risk, leaving us to make choices among imperfect alternatives. The real world is complex, but it's the one we have.

Donald Kennedy
Editor-in-Chief

10.1126/science.1119787

ILLUSTRATION: PAT N. LEWIS

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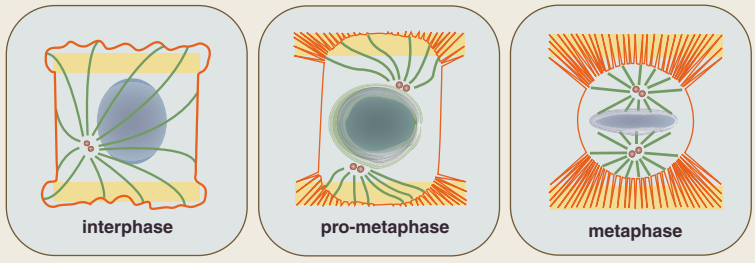
CELL BIOLOGY

Getting Oriented



Orienting the mitotic spindle; fibronectin (yellow), DNA (blue), and retraction fibers (red lines).

When cells within tissues divide, the orientation of the mitotic spindle defines the position of the daughter cells and thereby dictates cell fate. Théry *et al.* explored the relative effects of cell geometry and extracellular cues on how mammalian cells orient their division axis in vitro. Cells adhered to the substrate via interactions with the extracellular matrix (ECM), and the authors used micro-contact printing to lay down the ECM component fibronectin in well-defined patterns. By looking at how cells spread and divided on these surfaces, the authors found that the spatial organization of the ECM influences via retraction fibers the dynamics of the actin cytoskeleton, which then specifies the orientation of the division axis. This system can be manipulated to look at other regulatory inputs onto spindle orientation and hence daughter cell positioning, which may be useful in tissue engineering and device design. — SMH

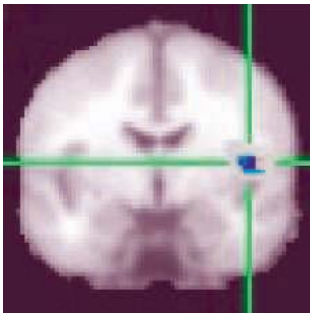
Nat. Cell Biol. 10.1038/ncb1307 (2005).

PSYCHOLOGY

It's Not Just in Your Mind

The links between psychology and immunology have, for the most part, either been dismissed as a collection of anecdotes or avoided as being too nebulous to study in a controlled fashion. The consequences have been a persistent interest in folk science and a dearth of solid mechanistic evidence.

Rosenkranz *et al.* have brought modern neuroimaging techniques to bear on this problem and identify neural substrates where the state of the body makes itself known to the mind. Six asthmatic patients were challenged with allergens (cat dander and dust mites), and the subsequent development of early-phase (mast cell degranulation) and late-phase (T cell cytokine release) airway constriction was measured by forced expiratory volume and sampling of sputum and blood after 1 and 4 hours, respectively. Concurrently, the neural responses to asthma-related words were assessed by brain scans. Under these conditions, activity (specifically associated with words such as wheeze) in the insula and the anterior cingulate cortex correlated with the extent of late-phase allergic inflammation, suggesting that physiological stress can influence the cognitive processing of emotionally potent stimuli. — GJC



Activation of the insula.

Proc. Natl. Acad. Sci. U.S.A. **102**, 13319 (2005).

EVOLUTION

Sex Doesn't Pay for Females

In the battle of the sexes—also known as sexually antagonistic coevolution—it is the female who loses. For instance, in *Drosophila,* males harm females during both courtship and mating. But are there hidden benefits for females; that is, do they endure the injury of multiple mating to benefit their offspring? And could such benefits compensate for the direct costs of mating?

Stewart *et al.* address the latter question in *Drosophila* by creating an artificial selection system that protects females from the cost of injury by males, but also robs them of any indirect advantages. A population of red- and brown-eyed females were briefly mated, and the nonvirgin flies were separated, so that the red-eyed females were subsequently exposed to a low density of harassing males (1:8, male:female) and the brown-eyed flies were exposed to a high density of males (1:1). Progeny from these crosses were collected and counted for eye color, and the experiment was repeated for five generations. The frequency of the red-eye "male resistance" allele increased substantially, showing that the indirect benefits of multiple mating (being able to trade up for a better mate) fail, by a considerable margin, to outweigh the harm inflicted. So why hasn't a real male resistance allele appeared? The authors speculate that males stay ahead of females in the sexual arms race and that females cannot anticipate male adaptations. — GR

Proc. R. Soc. London Ser. B 10.1098/rspb.2005.3182 (2005).

APPLIED PHYSICS

A Miniature Clock Factory

The combination of developments in microfabrication and precision spectroscopy of confined atomic gases has promised to benefit applications in timing metrology, where the requirements of low cost and small size along with long-term stability are paramount. However, earlier work on chip-sized atomic clocks has shown that chemical reactions in the gas cell, resulting from the presence of impurities and byproduct gases from the cell fabrication and gas-filling processes, lead to long-term drift in the clock frequency.

Knappe *et al.* have devised a fabrication and cell-filling technique that removes much of the contaminant gas from the cell, and they show that the frequency stability can be improved by several orders of magnitude to a drift of no more than 5×10^{-11} per day. The improvement suggests chip-scale atomic clocks as a viable technology in applications where better precision than that available in quartz-based clocks is desired. — ISO

Opt. Lett. **30**, 2351 (2005).

CREDITS: (TOP) THÉRY *ET AL., NAT. CELL BIOL.* 10.1038/NCB1307 (2005); (BOTTOM) ROSENKRANZ *ET AL., PROC. NATL. ACAD. SCI. U.S.A.* **102**, 13319 (2005)

ENVIRONMENTAL SCIENCE

Winter Advisory

Fresh water is one of the most important resources and is vital for humans, agriculture, and natural ecosystems. There are many threats to the supply of this commodity, including climate change; pollution by industrial, agricultural, and automotive wastes; and overuse. Kaushal *et al.* add another: road salt.

Road salt is used liberally in areas of the northeastern United States that receive appreciable amounts of snow, and the runoff into urban and suburban watersheds is a growing threat to fresh water reserves. By measuring the concentration of chloride in streams in Maryland, New York, and New Hampshire during winters, the authors show that salinities are approaching 25% that of seawater in some cases and are greater than 100 times that of pristine forest streams during summers. Watersheds where roads are densest are under severe pressure. If salinity in these regions continues to increase, surface water supplies in the Northeast may become unfit for human consumption and toxic to freshwater organisms by the end of the century. — HJS

Proc. Natl. Acad. Sci. U.S.A. **102**, 13517 (2005).

Baltimore County, Maryland.

CREDIT: BALTIMORE ECOSYSTEM STUDY LONG TERM ECOLOGICAL RESEARCH

CHEMISTRY

The Value of a Nickel

Ethylene and other terminal olefins are produced inexpensively and in large quantities from petroleum and can be used directly as electrophiles in reactions for making pricey chemicals. However, to use olefins as nucleophiles, it's generally necessary to transform them into air-sensitive lithium or magnesium organometallics.

Ng and Jamison have developed a homogeneous nickel catalyst for the direct addition of terminal olefins to aldehyde electrophiles, which leads to synthetically useful allylic alcohols without the need for metallation. The key to the catalyst is a hindered arylphosphine ligand. High yields are obtained at room temperature for the addition of ethylene to aromatic or tertiary alkyl aldehydes, coupled with silylation of the resulting alcohol by triethylsilyl triflate and quenching of the triflic acid byproduct by an amine base. The reaction also works for alkyl-substituted olefins, albeit with a drop in yield, and regioselectively affords the geminal addition product. The authors speculate that the mechanism involves a five-membered Ni-metallacycle intermediate. — JSY

J. Am. Chem. Soc. 10.1021/ja055363j (2005).

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Unmixing Memory and Desire

Recovering drug addicts often relapse after exposure to environmental or contextual cues that are associated with drugs. In a rat model system, the acquisition of cocaine-conditioned place preference (COC-CPP) depends on activation of the extracellular signaling–regulated kinase (ERK); it is blocked by inhibiting mitogen-activated protein kinase kinase (MEK), which normally phosphorylates and activates ERK. Miller and Marshall show increased phosphorylation of ERK in the nucleus accumbens core (AcbC, a midbrain region associated with cue-elicited drug seeking) in rats that had acquired COC-CPP. Infusion of a MEK inhibitor into the AcbC shortly before testing blocked COC-CCP–related behavior and the associated increase in ERK phosphorylation. Furthermore, rats that received a MEK inhibitor right after passing the test failed to exhibit COC-CCP when retested later and showed decreased activation of the AcbC ERK pathway. Thus, the authors conclude that disruption of memory reconsolidation blocks the expression of COC-CCP. Expression of the transcription factor Zif268 in the amygdala increases after reexposure to stimuli associated with self-administration of cocaine. In the study by Lee *et al.*, rats learned to associate a light with a cocaine infusion; the association is so potent that the light acquires a reward value of its own and supports instrumental learning. When paired with a memory reactivation session, Zif268 antisense DNA infused into the basolateral amygdala eliminated the ability of light to promote acquisition of a new behavior. — EMA

Neuron **47**, 873; 795 (2005).

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NetWatch

edited by Mitch Leslie

DATABASE

Molecular Pick Ax

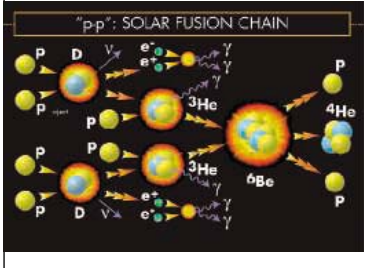
Knocking out genes is one way to decipher their function. Another method that's gaining popularity is chemical genomics: using small molecules to tweak biochemical pathways. To help researchers sift candidates for these experiments, the site ChemMine from the University of California, Riverside, profiles more than 2 million compounds from commercial suppliers and public databases such as the National Institutes of Health's PubChem. ChemMine's selling point is its many tools. You can track down molecules by structure, chemical properties, and activity; tease out similar compounds; and cluster the results by similarity.

bioweb.ucr.edu/ChemMine/search.php

EDUCATION

Fusion Fundamentals

Nuclear fusion could unleash 100 times more energy than nuclear fission and some 10 million times more than burning coal. Scientists haven't yet achieved a sustained fusion reaction, but students who want a quick introduction to this potential power source should check out FusEdWeb from Lawrence Livermore National Laboratory in California. A six-chapter primer explores everything from the main fusion reactions to different methods for creating the extreme temperatures necessary for atoms to merge. Stars depend on gravity, for example, but earthbound reactor designs use lasers, x-rays, and magnetic chambers. A glossary covers fusion and plasma terms. At left, the proton-proton chain that furnishes the sun's energy.



fusedweb.llnl.gov

IMAGES

Under the Volcano

Glowing chunks of lava tumble down the slopes of the Italian volcano Stromboli during a 2003 eruption. Located between Sicily and the Italian mainland, the restive mountain is one of the world's most active volcanoes, spurting debris several times an hour. Take a virtual hike up to the peak and excavate its geology and history at Stromboli Online, hosted by Italian researchers Roberto Carniel and Marco Fulle and Swiss teacher Jürg Alean. A primer traces Stromboli's formation from the time it pushed above the sea some 160,000 years ago. The volcano has been shooting off continually for about 2000 years, and spectacular photos and video record some of its recent blasts. Visitors can also probe the physics of eruptions with a simulator that calculates the trajectories of Stromboli's "bombs," partly molten lava globs.

Once you've scaled Stromboli, venture to other volcanoes around the world with the site's many multimedia tours. You can peer into Ethiopia's Erta Ale, which cradles a seething lava lake, and tour the Caribbean island of Montserrat, which the Soufrière Hills volcano devastated in 1995.

www.swisseduc.ch/stromboli

WEB PROJECTS

Hearing Test

All societies create music, but styles vary wildly, from Japanese kodo drumming to Tuvan throat singing to heavy metal. The Music Universals Study, composed by two Massachusetts Institute of Technology graduate students in cognitive science and media, aims to find out whether our perceptions of music depend on culture and experience by using the Web to survey people. You can play a part by completing the site's 15-minute test, which asks you to rate the pleasantness of sounds, indicate whether they evoke happiness or sadness, and determine whether the tension in a particular passage rises or falls. The students hope to have results from thousands of participants from different backgrounds and countries within a year.

music.media.mit.edu

DATABASE

Spiders Crawl Onto the Web

Arachnologist David Shorthouse of the University of Alberta in Edmonton, Canada, has found a fitting location for the server that houses his Nearctic Spider Database: the basement of his house. Visitors who scuttle over to this new clearinghouse can snare taxonomic and natural history data for about 350 of the roughly 3800 North American species, such as this ground-hunting wolf spider (below; *Pardosa xerampelina*). The accounts, provided by Shorthouse and other researchers, weave in information such as the creatures' distribution, habitat, anatomy, and diet. Shorthouse encourages other experts to add their data to the growing site.

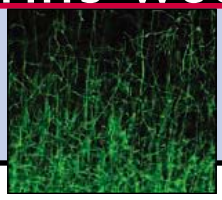
canadianarachnology.webhop.net

Send site suggestions to netwatch@aaas.org. Archive: www.sciencemag.org/netwatch

CREDITS (TOP TO BOTTOM): JÜRG ALEAN; CONTEMPORARY PHYSICS EDUCATION PROJECT; DAVID SHORTHOUSE

NEWS

This Week



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Stretching neural plasticity

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Chasing a new flu outbreak

U.S. BIOMEDICAL POLICY

NCI Head to Fill In at FDA After Crawford Resignation

The U.S. Food and Drug Administration (FDA), buffeted by scandals from the Vioxx withdrawal to the morning-after pill Plan B, endured more turbulence last week after its commissioner of 2 months suddenly quit. President George W. Bush further roiled the waters by tapping the leader of the country's war on cancer to be his temporary replacement.

On 23 September, Lester Crawford, 67, a decades-long veteran of FDA, resigned, citing his age. Within hours, Andrew von Eschenbach, 63, who has headed the $4.8 billion National Cancer Institute (NCI) for 3 years, was named acting FDA commissioner. Cancer specialists and several FDA watchers immediately expressed concern over von Eschenbach's appointment.

In particular, they worry about his plans to remain at the helm of NCI while overseeing FDA—a herculean task given the demands of each job, and one that could pose a potential conflict of interest. "I just don't know what [White House staff] were thinking," says David Johnson, who served on FDA's oncology drugs advisory committee and is deputy director of the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Senator Charles Grassley (R–IA) also questioned the decision, telling White House Chief of Staff Andrew Card in a 26 September letter that leading FDA is "not possible … on a part-time basis."

Two hats. Cancer Institute chief Andrew von Eschenbach has taken on a second job.

Von Eschenbach, a urologic surgeon, has stirred controversy in the cancer research community by setting a goal of ending cancer deaths by 2015. He has also fostered FDA-NCI collaborations and expressed interest in speeding the approval of cancer drugs. His appointment to FDA was greeted enthusiastically by two drug industry trade groups.

But some observers are puzzled by the president's decision to pick the head of another agency instead of someone within FDA, the traditional source for acting commissioners. "It strikes me as very odd," says oncologist Richard Schilsky of the University of Chicago, who sits on NCI's board of scientific advisers. In February 2004, Bush made a similar choice upon the surprise resignation of Rita Colwell at the National Science Foundation (NSF), calling on Arden Bement of the National Institute of Standards and Technology (NIST) to do double duty. Nine months later, Bement was nominated to lead NSF and, upon confirmation, resigned from NIST.

Ten scientists interviewed by *Science* questioned whether one leader, no matter how fluid a multitasker, can do justice to both organizations. In the short term, the arrangement could work, but "long term, I wonder whether it serves the best interests of all the constituencies," says Michael Friedman, a former acting commissioner of FDA who is now president and CEO of City of Hope, a cancer hospital in Duarte, California.

Even his former boss, M. D. Anderson Cancer Center president John Mendelsohn, worries about von Eschenbach's changing focus just as he hits his stride at NCI, which ▶

SCIENTIFIC COMMUNITY

Indians Embrace Science, But Can't Always Practice It

NEW DELHI—The first comprehensive study of India's emerging scientific workforce reports growing student interest in science—but sobering news about employment opportunities.

The *India Science Report*,* released this week, combines information from a massive public survey with data on the country's higher education sector. The $500,000 exercise, commissioned by the Indian National Science Academy (INSA) and executed through the National Council of Applied Economic Research in New Delhi, identified 8.74 million science graduates (those with college-level education in science). Another 1.8 million persons have advanced scientific and technical degrees, including 100,000 with Ph.D. degrees.

The welcome news, for Indian boffins worried about waning interest in science, is that the proportion of undergraduates pursuing science degrees has risen from 28.8% of the total enrollment in 1995–96 to 34.6% in 2003–04. Although the report's authors say that the reliability of the earlier data are questionable, the new data suggest that "the concerns about falling science enrollment in the country are misplaced." The data encompass the country's 200 universities and 12,000 colleges, which together spend more than $6 billion a year on research.

However, the same report raises a red flag about whether there are sufficient opportunities for those graduates to apply their knowledge. Some 22% of the country's jobless graduates hold science degrees, it reports, and a whopping 63% of those with advanced degrees but without jobs are in scientific fields. Although those percentages do not represent the unemployment rate for those categories of workers, it's still a troubling figure for a country that prides itself on being a burgeoning high-tech haven. "It's a wake-up call," says INSA President Raghunath Anant Mashelkar. "At the same time India is being projected as the next big knowledge superpower, the employability of people trained in science is low." —PALLAVA BAGLA

* insa.ac.in/html/home.asp

CREDIT: WWW.TOUROFHOPE.ORG

is trying to launch new initiatives while facing flat budgets. "It would be a shame to have him start all over on a new learning curve," Mendelsohn says. Observers also suggest that the dual appointment poses a conflict of interest. Because NCI is a major developer of cancer treatments, "it's a little curious for him to hold both jobs," says David Feigal, a former FDA devices official who is now a consultant.

Schilsky, however, suggests that von Eschenbach could delegate NCI-related decisions to others at FDA. FDA spokesperson Julie Zawisza said von Eschenbach was not available for interviews before *Science*'s deadline but noted that FDA is "looking very carefully" at possible conflicts of interest with respect to cancer drugs. "That will all be sorted out," she said. As *Science* went to press, federal officials had not explained how von Eschenbach would split his time between the agencies.

It's not clear when, or whether, the Bush White House will nominate a new FDA commissioner. Were von Eschenbach to remain in an acting capacity for long, he wouldn't be the first: Crawford sat in as acting head for 16 months before being confirmed by Congress in July. Since then, tensions between congressional Democrats and FDA have flared over the morning-after pill Plan B. In August, Crawford declined to decide whether Plan B could be sold over the counter. A week later, the head of FDA's Office of Women's Health, Susan Wood, quit, citing the agency's rejection of sound science in the Plan B case (*Science*, 9 September, p. 1671).

Legislators from both parties are already highly critical of recent FDA actions. Once the White House picks an official nominee, they are likely to start asking some tough questions.

–JENNIFER COUZIN AND JOCELYN KAISER

SCIENTIFIC COMMUNITY

Hurricane Rita Spares Major Research Institutions

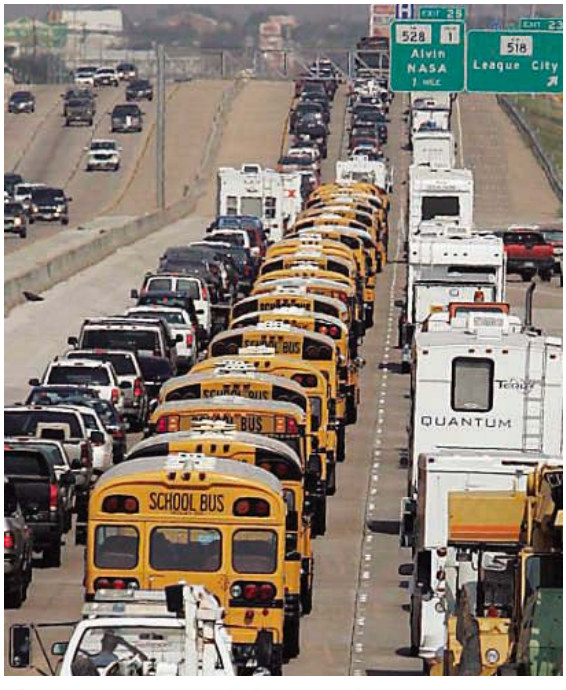
Scientists in Texas breathed a sigh of relief this week after Hurricane Rita weakened from its category 5 peak intensity and sidestepped Galveston and Houston. But the near-miss still allowed several major biomedical research institutions to field-test their procedures for weathering such a storm. "We really dodged a bullet on this one," says Larry Donehower, who researches aging at Baylor College of Medicine in Houston and lost thousands of mice to storm flooding in 2001.

Rita did trigger an evacuation of the area, shutting down universities and NASA's Johnson Space Center in Houston and forcing Donehower and other investigators to protect their research materials and data. The anxiety was heightened by recent events in New Orleans, where flooding and power outages following Hurricane Katrina took a heavy toll on research samples and displaced many researchers (*Science*, 23 September, p. 1980).

On the barrier island of Galveston, the site of one of the deadliest hurricanes in U.S. history in 1900, pre-Rita worries focused on the University of Texas Medical Branch's (UTMB's) highly secure labs for studying deadly infectious agents such as viruses that cause hemorrhagic fever. "We've thought about this for a long time, obviously," says Stanley Lemon, director of UTMB's Institute for Human Infections and Immunity. At biosafety level 3 labs and a smaller BSL-4 facility, researchers shut down experiments, autoclaved cultures, euthanized several hundred research mice, and fumigated labs, Lemon says. Samples were locked up in secure freezers plugged into backup generators and stocked with dry ice, and a skeleton crew waited out the storm. But Rita caused only minor damage to air handlers on the roof of a building with a shuttered BSL-3 lab. There will, however, be monetary "costs associated with shutting down experiments," Lemon says.

In Houston, research institutions bracing for Rita hoped they had heeded the lessons of tropical storm Allison. Flooding from that 2001 storm caused nearly $2 billion in damages at the Texas Medical Center and drowned more than 35,000 research animals at the complex's University of Texas Health Science Center (UTHSC) and Baylor College of Medicine (*Science*, 22 June 2001, p. 2226; 27 July 2001, p. 589).

UTHSC has since installed submarine doors in its medical school building, and animal facilities are no longer on ground floors, says spokesperson Scott Merville. At Baylor, there are still basement vivariums, but they now have "multiple layers of submarine doors," says President Peter Traber. The campus is also surrounded by a dike, with floodgates at entrances. Generators, once at ground level, now sit on higher floors.



Fleeing Rita. Texans, including researchers, faced traffic jams as they tried to evacuate coastal areas.

CREDIT: JAMES NIELSEN/AFP/GETTY IMAGES

As it happened, Houston received less than 3 centimeters of rain, and Baylor suffered no damage—"not even a broken window," says spokesperson Claire Bassett. "I was actually pretty confident we'd survive it okay," says Donehower. His group taped windows, covered computers, and left as the campus evacuated. All but one of the five people in his group turned back, however, after spending up to 9 hours inching along jammed highways. Donehower was back in the lab on Monday, and, he said, "everything is slowly returning to normal."

–JOCELYN KAISER

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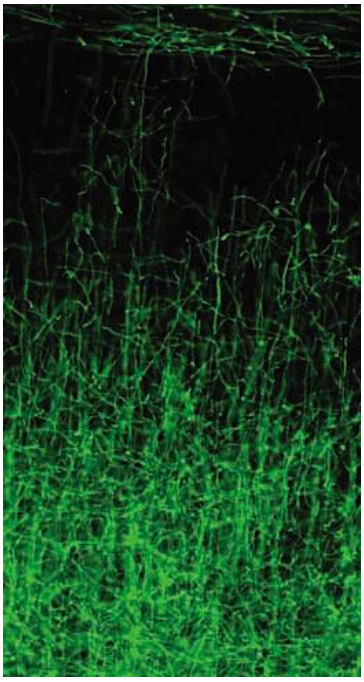
NEUROSCIENCE

Mutant Mice Reveal Secrets of the Brain's Impressionable Youth

In the malleable young brain, neurons readily adapt to new experiences by changing which cells they connect to and how they communicate with those partners. As the brain matures, it loses much of this neural plasticity and becomes considerably more set in its ways. On page 2222, researchers describe molecular signaling that may bring the brain's impressionable youth to an end. The identity of these maturity molecules may also shed light on the long-standing question of why it's difficult for the mammalian central nervous system to repair itself.

The researchers, led by Stephen Strittmatter of Yale University School of Medicine in New Haven, Connecticut, report that the brains of mice lacking a protein found on most cortical neurons, the so-called Nogo receptor, can adapt to the loss of sight in one eye long after the brains of normal mice have lost this ability. The findings represent the most dramatic demonstration so far that this type of neural plasticity, which normally is restricted to a critical period early in life, can be extended well into adulthood, says Michael Stryker, a neuroscientist at the University of California, San Francisco. "It's a very neat paper," he says.



Stabilizing influence. Myelin (*green*) may inhibit neural plasticity in the adult cerebral cortex.

CREDIT: AARON MCGEE AND STEPHEN STRITTMATTER

The work provides compelling evidence that the Nogo receptor plays an important role in brain maturation, says Martin Schwab of the University of Zürich in Switzerland. Researchers have studied the receptor primarily for its suspected role in limiting nerve regeneration after spinal cord injury and stroke. The new finding may resolve the mystery of what the Nogo receptor does in the healthy nervous system, Schwab says, by pointing to a general role for the receptor in stabilizing neural circuitry.

In the current study, Strittmatter and colleagues recorded the electrical activity of neurons in the visual cortex of normal mice and ones genetically engineered to lack the Nogo receptor. In normal mice and other animals, the visual cortex is evenly divided, with half its area more responsive to stimulation of the left eye, and half more responsive to stimulation of the right eye. But if one eye is sutured shut early in life, the open eye acquires more cortical territory, and the deprived eye loses out. In mice, this cortical land grab can only happen during a critical period that ends about 30 days after birth. Eyelid suturing after this time has no effect.

Not so, however, for mice lacking the Nogo receptor: When Strittmatter's team performed the eyelid suture on these mice 120 days after birth, well after sexual maturity, the rodents showed as much reorganization in their visual cortex as did normal mice sutured at 24 days. Similar experiments suggested that Nogo A, a component of the myelin insulation on neurons and one of several proteins that binds the Nogo receptor, is also a key player in inhibiting plasticity. A strain of mice lacking Nogo A exhibited plasticity in the visual cortex beyond the normal critical period.

Previous work has suggested that neurons in the visual cortex acquire their myelin insulation at about the same time as the critical period closes. To Strittmatter, this suggests that myelination precipitates the end of the critical period. Nogo receptor activation by Nogo A could prevent plasticity by preventing axons, the armlike extensions on neurons, from sprouting new connections, he explains.

"The conclusion that myelin is involved in locking down [neural] circuits is very exciting and … would finally provide a good physiological reason for why myelin is so chock-full of axon growth inhibitors," says Ben Barres, a neurobiologist at Stanford University in California. That case is far from proven, however. Barres points out, for example, that studies in different labs have yielded conflicting results about the importance of Nogo signaling for blocking axon growth. Replicating the current findings in mice that lack myelin would provide stronger support for Strittmatter's hypothesis, he says.

–GREG MILLER

ScienceScope

Congress Tackles Conflicts of Interest at FDA

U.S. senators last week unanimously agreed that the Food and Drug Administration (FDA) must do more to limit conflicts of interest on its advisory panels. But unlike their counterparts in the House of Representatives, who have sought an end to FDA waivers that allow individuals with conflicts of interest to serve on these panels (*Science*, 17 June, p. 1725), the senators have taken a more lenient view.

The measure, led by Senator Richard Durbin (D–IL), would require that FDA publish conflicts of interest on its Web site along with reasons for any waivers. In addition, Durbin and two colleagues—senators Mike Enzi (R–WY) and Edward Kennedy (D–MA)—asked the Government Accountability Office to examine how FDA selects advisory committee members. Advisory committees play a crucial role in determining whether drugs and devices for everything from cancer to heart disease should go on the market.

Ideally, anyone with industry ties ought not to vote on approving medical products, says Jerry Avorn of Harvard Medical School in Boston, but he notes that there are "gradations of allegiance" to pharmaceutical companies.

–JENNIFER COUZIN

Carbon Capture Probed

Storing carbon dioxide underground is an effective but expensive option to cut greenhouse gas emissions, the United Nations' Intergovernmental Panel on Climate Change said in a detailed report released this week. In recent years, scientists have studied whether industrial CO_2 emissions could be socked away in vast geologically formed underground reservoirs. Geological storage could hold 80 years' worth of current CO_2 emissions, says Bert Metz, co-chair of the working group that issued the new report. Local health and environmental risks would be minor. And the carbon will stay there, as the report finds underground carbon retention "likely" to exceed 99% over 1000 years.

But the report confirms long-standing worries that the storage option is expensive compared to reducing emissions through increased use of known technologies such as wind power. Metz says a CO_2 capture system would cost between 1 and 5 U.S. cents per kilowatt-hour for electricity. "There are cheaper ways" to reduce carbon emissions, says Metz. Experimental large-scale CO_2 geological storage projects have been established in Norway, Algeria, and Canada.

–PAUL WEBSTER

U.S. OCEAN POLICY

Proposed Fisheries Bill Falls Short, Critics Say

Overhauled. Administration bill isn't likely to restore the health of overfished Gulf of Maine cod.

One year after the second of two U.S. commissions called for an overhaul of the nation's ocean policy, proponents are still waiting for that needed sea change. Instead, what they got was an updated fisheries bill with some promising language but few real teeth.

The proposed legislation would reauthorize the 1976 Magnuson-Stevens Fishery Conservation and Management Act. It would set a 2-year deadline for halting catches of species clearly identified as overfished, permit regional fisheries councils to consider a whole-ecosystem approach to management, and create opportunities for scientists to become more involved in fisheries decision-making. "It's more definitive than the current law," says William Hogarth, director of the National Oceanic and Atmospheric Administration's National Marine Fisheries Service, which unveiled the legislation last week. "We've got a document on the table that will spur discussion."

But those changes are less impressive than they sound, say critics. The bill doesn't mandate that regional managers follow a whole-ecosystem approach, nor does it require authorities to use the scientific advice they are offered. And the bill actually relaxes the existing mandate that overfished stocks be off-limits and allowed to rebuild for 10 years, notes marine scientist Carl Safina of Stony Brook University in New York. "My guess is that most congressional members will not understand the context in which this is a setback," says Safina. "It will be spun and sold as if this is an improvement."

Marine biologist Ellen Pikitch is equally critical. "In my opinion, the bill does virtually nothing to advance ecosystem-based management in the U.S.," says Pikitch, executive director of the Pew Institute for Ocean Science in New York City and a member of the Pew Ocean Commission, which delivered its recommendations in June 2003, a year before the presidentially mandated U.S. Commission on Ocean Policy released its report. "It's necessary to mandate that the science be paid attention to," she says. "[If it isn't], I don't have a lot of faith that any of these other measures are going to have any effect."

The bill received a cautious endorsement from retired Admiral James Watkins, who led the U.S. Commission, and the head of the ▶

BIODIVERSITY

Indian Activists Release Disputed Report

NEW DELHI—Next week, an Indian advocacy group plans to release a massive report on biodiversity that the government commissioned but decided to shelve. It's the latest twist in a bitter battle over a 5-year study that the government once praised for its "highly participatory approach" and that outside experts see as a model for other nations.

The 1300-page report, entitled *Securing India's Future—Final Technical Report of the National Biodiversity Strategy and Action Plan*, was commissioned in 2000 by the Ministry of Environment and Forests to look at how the country should manage its rich biodiversity. It concludes that "India's model of development is inherently unsustainable and destructive to biodiversity." Needed improvements, it says, include more attention to the economic and human rights of traditional cultures and greater grassroots participation in government decisions that affect biodiversity.

Last December, ministry officials told Indian legislators that the report, which was submitted to the government early last year, should not be released because its "numerous discrepancies, scientific inaccuracies, and implausible and unacceptable recommendations" would subject the government "to great embarrassment and invite international ridicule and criticism." Shortly after, it wrote to Kalpavriksh, a nonprofit advocacy group based in Pune that has been a central player in the study, that the report "should not be published/distributed either in full or part thereof."

But Kalpavriksh plans to defy that order and release the report. "I don't see how such recommendations can damage India's reputation," says lead author Ashish Kothari, a sociologist working with the organization.

Seeing green. Managing India's rich biodiversity is a political flash point.

The report is part of India's obligatory response as a signer of the Convention on Biodiversity. The Global Environment Facility put up $1 million for the study, conducted through the India office of the United Nations Development Programme (UNDP). Kothari says that more than 50,000 people around the country were involved in the report, which includes both action plans and background papers.

UNDP's Jo Scheuer calls the process that produced the report "wonderful" and says it is regarded as an "international best practice" by the global biodiversity community. Ecologist Walter Reid, former director of the Millennium Ecosystem Assessment (*Science*, 1 April, p. 41), says that the Indian exercise "is one of the few that's been taken seriously and had a chance of making a significant impact. It would be a real tragedy if it was not used."

Ministry officials declined further comment on the status of the report. Kothari says that the document to be released next week corrects a few dozen "factual mistakes" contained in the final version. —**PALLAVA BAGLA**

With reporting by Erik Stokstad.

CREDITS (TOP TO BOTTOM): MASSACHUSETTS DIVISION OF MARINE FISHERIES; P. BAGLA

Pew Commission, former White House chief of staff Leon Panetta. Panetta says the legislation is, at least, an opportunity to "bring science into the issue." Both men say they are teaming up to increase pressure on Congress to adopt the overlapping recommendations in their reports. The key to a successful ocean policy, according to Panetta, will be to move beyond crisis management by investing sufficiently in ocean and coastal research.

The Magnuson-Stevens Act by itself can't solve all the problems facing the oceans, they say. What's needed is comprehensive legislation that coordinates both ocean and coastal issues. Anyone looking for a reason to change current U.S. ocean policy can point to Hurricane Katrina, says Watkins. That devastating storm exposed the lack of a coherent strategy to protect fragile coastal communities, he says. **–CAROLYN GRAMLING**

EPIDEMIOLOGY

Horse Flu Virus Jumps to Dogs

Mankind may be worried about a worldwide outbreak of influenza, but man's best friend is already in the midst of one. A dangerous flu virus originating in horses is spreading fast among U.S. dogs and may circle the globe, researchers say. Although the outbreak poses no direct threat to humans, "it's another example of what we fear most about flu viruses: They're always trying out new hosts," says Michael Perdue, an animal influenza expert at the World Health Organization in Geneva, Switzerland.

With very few exceptions, dogs seemed resistant to influenza, says Edward Kilbourne, a retired flu researcher at New York Medical College in New York City, who published rare evidence of a human flu strain infecting six dogs in New York in 1975.

Built for speed. A new flu virus, which first appeared among U.S. race dogs, is spreading fast among canines.

The current outbreak, described in a paper published online by *Science* this week (www.sciencemag.org/cgi/content/abstract/1117950), came to light after 22 greyhounds developed a respiratory disease—and eight died—at a Florida racetrack in January 2004. Cynda Crawford, an immunologist at the University of Florida's College of Veterinary Medicine in Gainesville, sent tissue samples from the infected dogs to Edward Dubovi at Cornell University, who isolated the influenza virus. A team led by Ruben Donis at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, then typed and sequenced the virus and studied its spread.

They found that it belongs to the H3N8 strain, which causes influenza in horses worldwide. Its sequence is 96% identical to that of other circulating H3N8 strains, suggesting that the entire virus jumped the species barrier, without reassorting with another strain first.

It appears to be spreading fast. Last year, 14 greyhound racetracks in six U.S. states reported respiratory outbreaks; in 2005, 20 tracks in 11 states did. Although the team did not investigate every outbreak, it found evidence of H3N8 wherever it looked. The team also reports that almost 80% of 70 dogs with respiratory disease in veterinary clinics and shelters in Florida and New York state were infected.

Based on archived serum samples from Florida race dogs, the team believes that the virus may have been in dogs at least since 2000; the very close resemblance among three dog isolates from 2003 and 2004 suggests that the virus made the jump only once. One mystery is why that happened only recently, because H3N8 has been found in horses for at least 40 years, says Thomas Chambers, an equine influenza expert at the University of Kentucky in Lexington. Whatever triggered the leap, Donis says, nothing seems to stand in the way now of a panzootic: the animal equivalent of a pandemic. Perdue says current horse vaccines should be easy to adapt for dogs and may be available soon.

Theoretically, the canine outbreak also gives the virus new chances to enter the human population. So far, there's no sign it has; nor has H3N8 been known to jump from horses to humans, Chambers says. The CDC researchers plan to test people who were in contact with sick dogs as soon as they have approval from an ethics panel. If any of them turns out to be infected—even asymptomatically—says Perdue, "that would raise a big red flag." **–MARTIN ENSERINK**

CREDIT: ANDY MUELLER/REUTERS

ScienceScope

Academic Grants at Issue

A House committee wants to know whether university scientists are misusing research funds from the National Institutes of Health (NIH). Last week, representatives Joe Barton (R–TX) and Ed Whitfield (R–KY) of the Committee on Energy and Commerce asked the inspector general of the Department of Health and Human Services to examine how NIH grantees are spending their money. A second letter sought an investigation into overcompensation of graduate students at state universities following allegations of such practices at the University of California.

The congressional request follows a half-dozen settlements by universities in cases involving charges of misuse of federal funds over the last 2 years. Harvard, the Mayo Clinic, Cornell, and others have made payments ranging from $2.4 million to $6.5 million after charges of falsifying time accounting, diverting money from one grant to another, and spending grant money on patient care. All settled with the Department of Justice without admitting wrongdoing. In August, the *Wall Street Journal* chronicled the Cornell case in a story, piquing the House Committee's interest.

NIH hasn't changed its oversight of grants because of the settlements and doesn't expect the probe to turn up much, says Norka Ruiz Bravo, NIH deputy director for extramural research: "We don't think we have a lot of problems." **–JENNIFER COUZIN**

U.K. Stargazers: Save the Leap Second

Astronomers in the United Kingdom are fighting a proposal before to the International Telecommunication Union (ITU) to abolish the venerable leap second. Leap seconds, added once every 500 days or so, keep high-precision atomic clocks from running ahead of solar time, which is gradually falling behind as tidal friction slows Earth's rotation. Clock resetting happens irregularly, says U.S. delegate Ronald Beard of the Naval Research Laboratory, and could potentially affect systems for air traffic control or economic transactions. But astronomers, led by the Royal Astronomical Society (RAS), say the leap seconds are integral to the programs that align telescopes and track satellites, so a change would require an expensive overhaul. "Otherwise, you could point your telescope in the wrong place," says Mike Hapgood of RAS. In November, ITU will debate the proposition, but a final decision could take years.

–MICHAEL SCHIRBER

NEUROSCIENCE

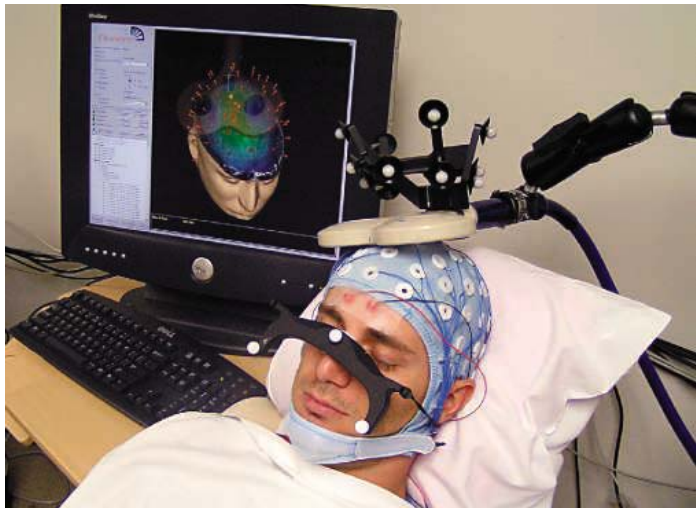
Neural Communication Breaks Down As Consciousness Fades and Sleep Sets In

By using magnetic pulses to stimulate the brains of waking and sleeping volunteers, scientists may have gained an important insight into the age-old mystery of why consciousness fades as we nod off to sleep. In a report on page 2228, a research group at the University of Wisconsin (UW), Madison, concludes that as sleep sets in, communication between different parts of the cerebral cortex breaks down. Such communication is a likely prerequisite for consciousness, the team argues.

Some, but not all, neuroscientists find the team's evidence compelling. The research "definitely tells us something about sleep and may have important implications for understanding the neural correlates of consciousness," says Christof Koch, a cognitive neuroscientist at the California Institute of Technology in Pasadena.

Early neuroscientists assumed that consciousness wanes during sleep because the cerebral cortex simply shuts down. "In the last century, we had three Nobel Prize winners who thought that the cerebral cortex is completely inhibited during sleep," says Mircea Steriade, a neuroscientist who studies sleep at Laval University in Quebec, Canada. Electroencephalography (EEG) and other methods have since ruled out that explanation, showing that the electrical chatter and metabolism of neurons in the cortex continues unabated during sleep. That left neuroscientists puzzling over why consciousness fades when the brain is still active.

Giulio Tononi of UW has spent years developing a theory that the essence of consciousness is the integration of information. Communication between different regions of cortex might be one sign of this integration—and of consciousness, Tononi says. To test that idea, he and his team recorded electrical activity in the brains of six sleepy volunteers using high-density EEG. Before the subjects nodded off, the researchers stimulated a small patch of right frontal cortex with transcranial magnetic stimulation (TMS), a noninvasive method that uses magnetic pulses to induce an electrical current inside the head. The ▶



Drifting off. Magnetically stimulating the brains of sleeping volunteers may provide clues about the nature of consciousness.

CRYPTOGRAPHY

Simple Noise May Stymie Spies Without Quantum Weirdness

With the grand ambition of sending unbreakable coded messages, some physicists are using exotic tools—streams of individual photons and quantum mechanics—to shut out prying eyes. But a wire and a few resistors may convey a message as securely, says a physicist who has devised a simple and—he claims—uncrackable scheme. The idea shows that "classical" methods might compete with budding "quantum cryptography," others say. "I believe in beautiful and simple ideas, and this is one of them," says János Bergou, a theorist at Hunter College of the City University of New York.

Stealth technology. A simple wire and resistors may send data securely.

Take the hypothetical secret sharers, Alice and Bob: They transform a message into binary numbers and use a numerical "key"—a secret string of random 0's and 1's—to scramble and unscramble it. Quantum cryptography allows them to pass the key under the nose of an eavesdropper, Eve, because she cannot measure the condition of a particle without affecting it. So if Alice and Bob encode the key in individual photons, Eve cannot read it without revealing herself.

But Alice and Bob might do just as well by measuring the electrical noise on the ends of a wire, says Laszlo Kish of Texas A&M University in College Station. In Kish's scheme, Alice and Bob have two resistors each, one with a big resistance and one with a small resistance. Each randomly connects one resistor or the other between his or her end of the wire and ground and measures the voltage between the wire and ground.

On average, that voltage is zero. But electrons in the resistors jiggle about with thermal energy, so the voltage fluctuates, and the size of the fluctuations, or "Johnson noise," depends on the resistances Alice and Bob choose. If both use the large resistance, the fluctuations will be big. If both use the small resistance, they will be small. And if one uses large and the other uses small, the noise takes an intermediate value.

Eve can measure the fluctuations, too. But when the noise is at its intermediate level, she cannot tell whether Alice or Bob has chosen the large resistance unless she injects a current, which will reveal her presence, as Kish describes in a paper posted on the Web site www.arxiv.org and submitted to the journal *Physics Letters A*. So Alice and Bob can use the large-small pairs to generate the key.

Making the scheme work over long distances may not be easy, says Weston Tew, a physicist at the National Institute of Standards and Technology in Gaithersburg, Maryland. And Bergou notes that if the wire itself has a sizable resistance, then the fluctuations should be slightly larger on the end with the large resistance, a fact Eve might exploit if she spies on both ends at once. Still, today's quantum technologies only approximate the uncrackable ideals, and Kish's idea suggests that simpler schemes might match their performance, says Julio Gea-Banacloche, a theorist at the University of Arkansas in Fayetteville. "The more I think about it," he says, "the more I think that within limits it's workable."

—ADRIAN CHO

CREDITS (TOP TO BOTTOM): M. MASSIMINI *ET AL.*, *SCIENCE*; PHOTODISC BLUE/GETTY IMAGES

EEG record revealed how the neural activity triggered by TMS spread from the site of stimulation to other parts of the brain. The team repeated the experiment once the subjects had entered non–rapid eye movement (non-REM) sleep. Noise-canceling earphones ensured that subjects couldn't detect the sound of the TMS magnet.

When the subjects were awake, TMS elicited waves of neural activity that spread through neighboring areas of the right frontal and parietal cortex and to corresponding regions on the left side of the brain. During non-REM sleep, the same TMS stimulus only elicited neural activity at the site of stimulation.

Tononi says the findings suggest that different areas of cortex do indeed stop talking to each other during non-REM sleep—a stage of sleep in which people often report little or no conscious experience on waking. An important follow-up, he says, will be to repeat the experiments during late-night REM sleep, when people report consciouslike experiences in the form of dreams. "We would predict a pattern which is much more similar to wakefulness," he says.

Linking cortical connectivity to consciousness makes sense, says Rodolfo Llinas, a neuroscientist at New York University. A key feature of consciousness is the ability to integrate many aspects of an experience into a single perception—combining red petals, rosy scent, and prickly thorns into the perception of a rose, for example. "To make an object in your head, to make one single cognitive event, you have to bind the activity of many cortical areas," Llinas says.

But not everyone accepts Tononi's conclusions. The experiments are "very elegant and pretty," but their relevance to understanding consciousness is questionable, says Robert Stickgold, a neuroscientist who studies sleep at Harvard Medical School in Boston, Massachusetts. "There are many, many differences in brain chemistry and physiology … between wakefulness, non-REM sleep, and REM sleep," including differences in neurotransmitter and hormone levels and patterns of neural activity, Stickgold says. The change in cortical communication is yet another such difference, he agrees, but there's no convincing evidence that it's the key to fading consciousness. **–GREG MILLER**

HIGH-RISK RESEARCH

Six Women Among 13 NIH 'Pioneers'

The résumé of evolutionary psychologist Leda Cosmides of the University of California, Santa Barbara, proudly lists that she was a finalist in last year's inaugural competition for the 5-year, $2.5 million Pioneer Award from the National Institutes of Health (NIH), even though she didn't win a penny. In fact, there were no women among the nine winners, an omission that triggered complaints of gender bias (*Science*, 22 October 2004, p. 595).

What a difference a year makes. This week, Cosmides, 48, and five other women join an elite group of 13 scientists chosen for the 2005 Pioneer Awards,* which NIH Director Elias Zerhouni says are designed for "exceptionally creative scientists taking innovative approaches to major challenges in biomedical research." The dramatic shift in gender composition was not a goal of the selection process for the second competition, says Jeremy Berg, director of the National Institute of General Medical Sciences, who oversaw the competition. But, he says, NIH did make a very deliberate attempt to level the playing field.

"Women, underrepresented minorities, and early-career scientists were especially encouraged to apply," Berg says. Accepting only self-nominations (rather than institutional submissions) may also have helped remove any subtle advantages, he adds. He says NIH spent more time schooling its reviewers, who last year were overwhelmingly male, on the importance of looking for the best people with the most exciting ideas. Having fewer applications this year—some 840 compared with 1300 in 2004—also made the three-tiered review process go more smoothly, he notes. The result was not only a better gender balance but also a younger cohort represented by 35-year-old Nathan Wolfe, a tenure-track molecular epidemiologist at Johns Hopkins University in Baltimore, Maryland, who spends the majority of his time working with hunters at a Cameroon field station in search of zoonotic diseases in the early stages of adapting to humans.

Award winners. Leda Cosmides and Peter Harbury are part of a baker's dozen whose proposals wowed NIH judges.

CREDITS (LEFT TO RIGHT): MIRANDA SAVANI; P. HARBURY

For Cosmides, the award represents further affirmation for a field that she and her husband, John Tooby of Harvard University, helped establish in the early 1980s. "Those were tough years," she recalls. "Something like this at the beginning of our work would have been a godsend. I can't say enough about what NIH is trying to do [with this award] to encourage novel work across disciplinary boundaries."

Stanford University neuroscientist Ben Barres, a vocal critic of last year's awards, says he was "deeply impressed by how NIH revamped the process this year." As it happens, he also chaired the final round of face-to-face, 1-hour interviews on the NIH campus, at which he says "gender or race issues" never surfaced. But the quality of the science being proposed blew him away, he adds.

Pehr Harbury worried that he'd blown his chances when his laptop swallowed his PowerPoint presentation during a cab ride to NIH. But the 40-year-old Stanford biochemist, who received tenure just last year, needn't have worried. Not only did his description of applying computer-generated small molecules to design a vast new class of potential drugs impress the NIH judges, but 1 day after winning a Pioneer Award, Harbury learned that he had also been awarded a so-called genius grant—and $500,000 with no strings attached—from the John T. and Catherine B. MacArthur Foundation.

"I feel a little guilty," he confessed. "I've been scraping along [NIH had rejected his first six single-investigator proposals, and he currently has one R01 for his six-person lab], and the MacArthur prize is for people having trouble getting funding. And now I have more money than I ever imagined."

–JEFFREY MERVIS

* nihroadmap.nih.gov/pioneer

Congress is poised to revise a 1973 law that critics say hasn't worked and that defenders say needs to be strengthened. What has it done for the species on the list?

What's Wrong With the Endangered Species Act?

The California gnatcatcher needed help. With more than 80% of its habitat gone by the late 1980s and populations plunging, the diminutive songbird that lives in coastal sage scrub in southern California seemed to birders and environmentalists to be a deserving candidate for listing under the Endangered Species Act (ESA).

The birds' decline was equally alarming to land developers, but for a different reason. Worried that invoking the act might put a stop to new housing and other development on valuable real estate, some developers challenged the U.S. Fish and Wildlife Service's (FWS's) proposal in 1991 to list the gnatcatcher. And although they lost a 2-year court fight, their arguments shaped the 1993 decision by the government to grant protection to the bird.

Specifically, federal officials drafted a rule that allowed some birds to be harmed as long as the developers participated in an innovative state planning program. The goal was to coordinate conservation of larger blocks of habitat and encourage conservation not just on federal land but also on private lands, where most of the birds are thought to live. But although the plan has lessened conflict, it didn't end it. Some environmental groups felt that developers were given too much leeway, and they successfully sued FWS again to win further protection for the gnatcatchers' habitat.

And what has become of the gnatcatcher? Some 15 years after its plight was first addressed, biologists think it has a good shot at survival. But no one knows exactly how the bird is faring—or whether it has a better chance because of the listing.

Such is the uncertain, conflicted world of the ESA. Passed in 1973, it's been called the strongest conservation law in the world. Yet it has serious flaws. The ESA forbids anyone from harming the gnatcatchers, for example, but it doesn't mandate helpful actions, such as enlisting landowners in a recovery effort. In addition, clear measures of success are hard to come by. Even when the law motivates conservation partnerships among public and private organizations, it's rare to know how much—or even whether—species are benefiting. At the same time, the act has upset private landowners and frustrated businesses. And never-ending legal battles have drained scarce resources from conservation efforts.

Saving Habitat

Last refuge. Embattled by development, species such as the California gnatcatcher sometimes require flexible plans to encourage conservation on private lands.

Citing these and other problems, opponents say it's time to admit that the act has been a failure at helping species recover. Last week, Representative Richard Pombo (R–CA), chair of the House Resources Committee, introduced a bill that would substantially revise several provisions in the act. The goal, he says, is to ease the burden on landowners and businesses. "Without meaningful improvements, the ESA will remain a failed managed-care program that checks species in but never checks them out," Pombo said in a statement, alluding to the fact that few species have graduated from the endangered list. "This bill will remove the impediments to cooperation that have prevented us from achieving real results for species recovery in the last 30 years."

Environmentalists don't accept Pombo's assessment of ESA's performance. The fact that 99% of the 1268 species listed are still surviving, they say, shows that the act is taking care of business. They fear that many of Pombo's changes would weaken the act's ability to protect endangered species. "We were very disappointed" by Pombo's bill, says Jamie Rappaport Clark of Defenders of Wildlife, a former chief of FWS. "It will not only undermine species recovery but lead to more extinctions."

Clark and others want Congress to make the ESA more capable of putting imperiled species on the road to recovery. A large infusion of funds is vitally needed to help federal agencies clear up a backlog of pending listings, handle the vast amount of administrative work needed to implement a listing, and carry out on-the-ground conservation actions. Failing that, they say, legislators should at least streamline procedures for listing and improve the recovery planning process. "I'm not convinced that at this point we need to tinker with the act," says ecologist Gordon Orians of the University of Washington, Seattle. "We need to put more money into it."

The long-awaited bill is on an extremely fast track. Pombo's committee approved the bill barely 24 hours after holding a hearing, and the entire House of Representatives could do the same as early as this week. That pace has irked moderate Republicans, who say they need more time to study the bill. The Senate is moving more slowly, however, and is not expected to take up a comparable measure before next spring.

A growing backlog

Enacted in 1973, the ESA amplified the powers of a similar law passed in 1966. It's

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intended to prevent landowners, private or federal, from doing anything—building a house or a road, logging a forest, etc.—that would harm a listed species. "It's an innately powerful law," says Lance Gunderson of Emory University in Atlanta, Georgia. "Some people call it the pit bull of legislation." As a result, adds Dan Rohlf of Lewis & Clark Law School in Portland, Oregon, "the ESA has put conservation on the table in a lot of places where it would never have been on the table."

Unfortunately, in many cases the action takes place in a courtroom. For opponents of the act, the first response to a proposed listing is typically a suit claiming that the scientific underpinnings for the FWS decision are weak. As of this month, FWS was engaged in 61 lawsuits related to various aspects of the listing process. It's also dealing with court orders in 51 other suits.

Pombo and other opponents say they want to strengthen the scientific judgments upon which agencies act by requiring listings to meet more rigorous standards of evidence. They point to the 15 species that have been delisted after subsequent research revealed that populations were actually more robust than previously thought, and the 39% of listed species whose status is unknown (see data box, p. 2152). FWS now uses the "best available science" in deciding whether to list a species and determine its status; Pombo's bill calls for the Interior and Commerce secretaries to define what "best" means.

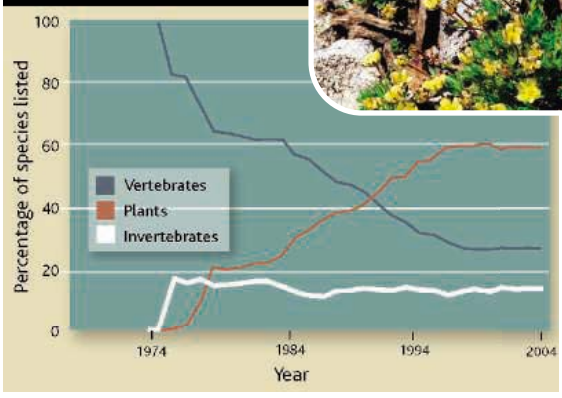
Environmentalists object to that change. They say such political appointees could set the bar prohibitively high, especially if little is known about a species. Congress intended the act to be precautionary, they say: When extinction is at stake, it's better to be safe than sorry.

Despite that mandate, FWS has had a difficult time adding species to the list. A historical rate of listing roughly 40 species a year has fallen to only about 13 during the 4.5 years of the Bush Administration. The backlog is sizable, with 286 "candidate" species on the FWS waiting list. On average, these candidate species have been waiting for 17 years. And since 1973, 27 species have gone extinct while on this list.

The current waiting list is likely just a fraction of the real backlog. According to NatureServe, a nonprofit clearinghouse for conservation biology, more than 9000 species in the United States are eligible for ESA listing. The waiting list could swell considerably if the agencies begin to put more emphasis on invertebrates and plants. "There are far more species at great risk than we think," says James Carlton, a marine ecologist at Williams College in Massachusetts. "It is hard to be hyperbolic about that."

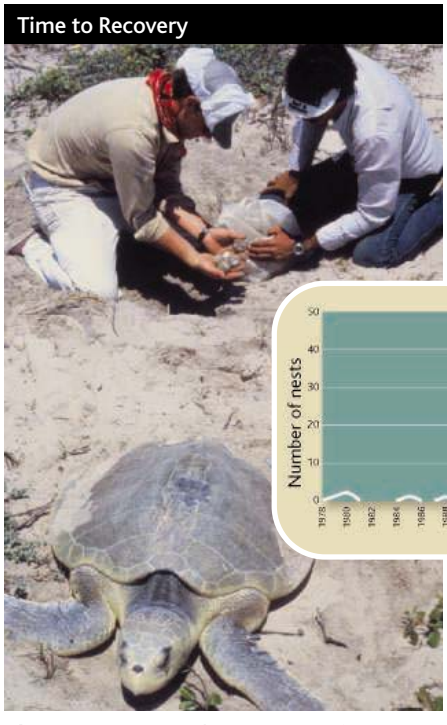
FWS readily admits that the magnitude of the backlog is a problem. But it pleads poverty as the main reason. In 2003, the agency estimated that just processing the candidate species would cost $153 million; yet it received $16 million for FY 2005 for all listing activities. That budget must also cover legal costs. In 2003, two-thirds of FWS's listing budget was spent on dealing with lawsuits and court orders. Environmentalists retort that the agency hasn't asked for what it needs. And delays matter. The prospects for recovery of a declining species become dimmer and more expensive over time.

What to Protect



Going green. Plant lovers have boosted the flora on the list, such as the Robbins' cinquefoil, which was delisted in 2002. But there's less help for imperiled invertebrates.

Time to Recovery



Slow progress. It took many years of conservation efforts before the populations of Kemp's Ridley sea turtle began to rise.

A rocky recovery

For species that have been listed, proponents insist, the act is helping to stave off extinction. A prime example is the California condor, listed in 1967. It would never have survived without the legal protection and tens of millions of dollars provided by the act, says Michael Scott of the U.S. Geological Survey in Moscow, Idaho, who ran the program from 1984 to 1986.

Only nine listed species have gone extinct, and many were effectively doomed by the time they were listed. It could have been worse: In 1999, Mark Schwartz of the University of California, Davis, made a back-of-the-envelope estimate that roughly 190 species would have gone extinct without the act.

The act has been much less successful at helping species fully recover. Before species can be taken off the list, they must have healthy populations and adequate habitat. FWS has determined that nine species have reached that mark, all with threats that were relatively easy to address. For bald eagles, the biggest threat was DDT, which weakened their eggshells, and a 1972 ban on using DDT paved the way for their recovery.

For most species, however, recovery is still a distant goal. In 2002, just 6% were improving, and only 2% have accomplished more than 75% of the goals spelled out in their recovery plans. Scientists pin that poor record on the precarious state of most species when they were listed and inadequate recovery actions, not ESA itself. "Recovery will require many more decades than the three that the act has been in existence," says Michael Bean of Environmental Defense in New York City. Kemp's Ridley sea turtles, for example, which were listed in 1970, require 15 years or more to reach maturity and to begin reproducing once researchers release hatchings.

The first—and the most controversial—step toward recovery, according to the act, is for FWS to designate so-called critical habitat. The law defines this as an area essential for helping a species recover. Critical habitat affects only the actions of federal agencies, which must consult with FWS or the National Oceanic and Atmospheric Administration (NOAA) if a proposed action—a timber sale, say, or highway construction—will harm the critical habitat of a listed species. Yet many landowners still fear that designation will restrict their actions, delay projects, or decrease property values. Such disputes usu-

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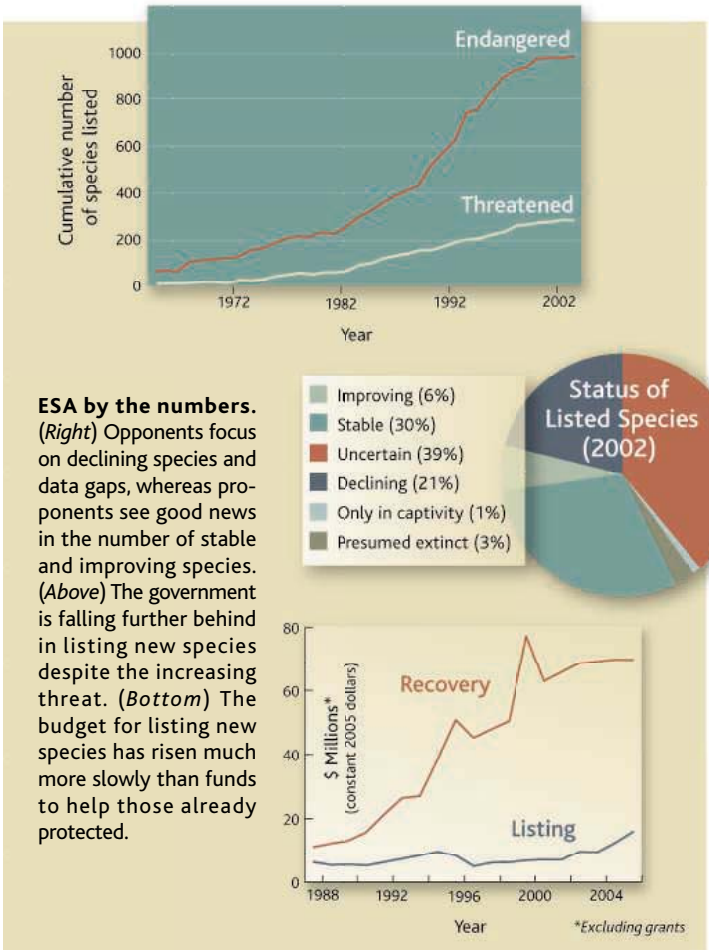
ally end up in court, tying the agency in knots and delaying other conservation actions.

FWS and NOAA have been extremely reluctant to designate critical habitat. Since 1981, they have maintained that the process eats up time and money without providing any additional protection to listed species. The reason, they say, is that the ESA already prohibits harm to listed species, and that degrading the critical habitat amounts to the same thing.

Although there's no doubt that species need habitat, the scientific evidence for benefits from officially designating critical habitat is not clear. Two studies that analyzed the same data in different ways have found that designation hasn't correlated with improved recovery. Environmental groups say that critical habitat does matter and point to a third paper, published in April in *BioScience*. In that paper, Kieran Suckling of the Center for Biological Diversity, an advocacy group based in Tucson, Arizona, and colleagues reported that species for which a designated critical habitat had been delineated for 2 or more years "were more than twice as likely to have an improving population trend in the late 1990s, and less than half as likely to be declining in the early 1990s."



ESA by the numbers. (*Right*) Opponents focus on declining species and data gaps, whereas proponents see good news in the number of stable and improving species. (*Above*) The government is falling further behind in listing new species despite the increasing threat. (*Bottom*) The budget for listing new species has risen much more slowly than funds to help those already protected.

The act requires FWS to designate critical habitat within a year of listing a species. But FWS rarely does because it feels that the designation is redundant. The missed deadlines have led to a series of successful suits by environmentalists, including a decision last year by a federal circuit court that the FWS interpretation of critical habitat needs to promote the recovery, not just the survival, of listed species. Rohlf of Lewis & Clark says that decision would add teeth to steps spelled out in recovery plans drafted by FWS, which are currently unenforceable. Pombo's bill would negate that ruling by repealing the statutes for critical habitat.

Money matters

Supporters say that the biggest obstacle to recovery for listed species is limited resources for implementing recovery plans—FWS documents that not only lay out the goals and methods for improving the population but also the amount of time and money the agency thinks will be required. In a 2002 *Bioscience* paper, Julie Miller of the University of Montana, Missoula, and colleagues found that birds and mammals were getting only about 50% of what had been recommended in recovery plans between 1989 and 1995, and that plants received just 20%. Boosting the current investment by about 25% for species on the list in 1999, they found, would have required almost doubling the recovery spending, from $350 million to $650 million. The study also found, as have others, that species that receive more dollars tend to do better.

Pombo's bill wouldn't give agencies any more money. In fact, their budgets could shrink under a provision that would require agencies to compensate landowners for the fair market value of any development or other activity that the government vetoed because it would impact endangered species. The bill doesn't estimate the annual cost of such payments but specifies that the Interior Department must pay them. Suckling worries that these settlements could easily consume FWS's $143 million budget for its endangered species program.

Despite the disagreement about whether to compensate owners for lost opportunities, all parties agree that conservation efforts would be aided by boosting incentives for landowners to help recover species. More than half the species on the ESA list have at least 80% of their habitat on private lands. Although the act can prohibit property owners from harming a species, it can't force them to help by, say, removing an invasive species that is causing trouble. That's why in the last 10 years FWS has significantly expanded the use and funding of agreements called Habitat Conservation Plans (HCP). Since 1982, the number of these plans has risen to almost 500.

HCPs allow the "take"—harming or killing of listed species—as long as the landowner has a plan in place for mitigating the effect. Some environmentalists support this approach, but others worry that the HCPs don't go far enough to bolster recovery efforts or even to monitor the status of species (*Science*, 13 June 1997, p. 1636).

One controversial feature of the HCPs, in effect since 1995, is a "no surprises" clause that locks the current plan in place. Critics say it doesn't account for further declines or the discovery of additional endangered species. They would also like to see more oversight and proof that voluntary agreements help listed species. Supporters, in turn, complain that getting these agreements in place, and funded, is cumbersome and slow.

Pombo's proposal would turn the "no surprises" policy into law and thereby increase the public's confidence in the certainty of the regulatory process. But the bill would ease regulations in some worrisome ways, critics say, for example, by allowing projects that might harm endangered species to go forward unless federal agencies object within 180 days. "The FWS couldn't possibly deal with all the requests" in that time frame without new resources, says Bean. "This runs the risk of foregoing the opportunity to constrain a whole host of development that could wipe out species."

Although the act is the most powerful tool available for halting actions that could harm species, it's become clear over 3 decades that its regulatory hammer isn't enough. Many environmentalists agree with Pombo that landowners must be encouraged to find new ways to protect species and lessen their reliance on litigation. But in making those changes, the bill would also weaken the act's regulatory authority. Opponents are hoping that the Senate will do less damage to those powers when it takes up the issue. But it seems unlikely that the final product, without cash to back it up, will significantly improve prospects for endangered species. **–ERIK STOKSTAD**

SOURCE: U.S. FISH AND WILDLIFE SERVICE

Agencies Hope to Cash In on the Allure of Competition

In the wake of the Ansari X Prize for space travel, U.S. science policymakers see prizes as a way to stretch tight budgets and uncover new talent

When Charles Lindbergh landed the Spirit of St. Louis in Paris in 1927, he did more than win a permanent place in aviation history. He also pocketed a $25,000 prize put up by a New York hotel owner for the first person to fly nonstop across the Atlantic Ocean.

Three-quarters of a century later, the U.S. government has caught prize fever. Next week, teams from academia and industry will compete for a $2 million award from the Defense Advanced Research Projects Agency (DARPA). The agency is offering the prize for an autonomous robotic vehicle that can complete a rugged course in the U.S. Southwest. Twelve teams have signed up to face off in Mountain View, California, on 21 October for $100,000 in prize money from NASA for designing the best mechanical climbers and space tethers. This summer's massive energy bill created prizes totaling up to $15 million at the Department of Energy (DOE) for fundamental and applied energy research. And in June, the House of Representatives told the National Science Foundation (NSF) to dream up a prize program "to focus on high risk/high payoff research."

Off road, on campus. Cornell students hope to qualify Titan for this year's DARPA Grand Challenge Race.

CREDIT: CORNELL UNIVERSITY

What's making U.S. lawmakers and federal officials so prize-happy is the chance to tap into the creative talents of a vast pool of techno-entrepreneurs they might not otherwise reach—and for relatively little cost. Cash prizes also give tight-fisted federal bureaucrats a chance to piggyback on the investment of others, as well as paying the piper only when—and if—a specific milestone has been achieved. That contrasts with a grant, in which the funds are disbursed ahead of time for something that may never pan out, or a contract, in which the government picks a person or institution to conduct research or deliver an agreed-upon product. "As opposed to the government looking into its crystal ball and choosing one [contractor] based on a bunch of technical proposals, this way it's more of a survival of the fittest," says NASA official Ken Davidian.

But as the idea wins support, some are asking whether prizes make sense for a basic research agency such as NSF. And others worry that they might put blinders on academic scientists by steering them toward defined challenges.

Cash on delivery

The renewed popularity of technology prizes owes a debt to airplane designer Burt Rutan, who won $10 million last summer for soaring into space on a privately funded craft. Whereas the public was enthralled by the drama and risk of that competition, federal officials admired its financial advantages. Teams spent anywhere from $100 million to $400 million competing for the Ansari X Prize, organizer Peter Diamandis told Congress last summer. And the beauty of the prize, he said, is that "we don't pay … a single dollar until someone does it." The prize money came from space enthusiasts, corporate sponsors, and an innovative hole-in-one insurance policy.

It's probably no surprise that DARPA, an agency with a reputation for taking fliers in pursuit of the latest military technology, is leading the way. In 1999, then–DARPA general counsel Richard Dunn led an effort to get permission from Congress to offer prizes as part of a larger campaign to loosen rules for defense research contracting. He says his goal was to broaden the agency's list of contractors to include "people out there that didn't want anything to do with the government."

DARPA officials say their first use of the prize, last year's autonomous vehicle race, proved the value of that approach despite the fact that none of the 15 vehicles traveled more than 11 km of the 229-km course across the Mojave Desert in California. DARPA chief of staff Ron Kurjanowicz says that having so many teams tackle the problem yields a wealth of ideas for technologies that might apply to the battlefield. One example: Some teams load their vehicles with detailed geographic maps, while others save on computing power and rely on sensors gathering data as they go.

Industry participants say the prizes stimulate the development of potential new products as well as providing good public relations. John Schwartz, a spokesperson for Oshkosh Truck Corp., says the company's $2-million-plus investment in the DARPA race has enhanced an existing effort to develop cost-effective bolt-on systems that might one day operate robotic military trucks.

NASA officials also wanted to expand their talent pool beyond tried-and-true contractors such as Lockheed and Boeing to include people like Flint Hamblin, a competitor in the climber challenge, who designs amusement park rides for a living. Washington, D.C., bureaucrats don't always know where to look for the next breakthrough, says NASA official Brant Sponberg. "No one was betting on Charles Lindbergh," he says.

Basic questions

But skeptics—including some lawmakers—worry about possible unintended side effects of shifting federal resources into science and technology prizes. With the cost of the war in Iraq and Hurricane Katrina recovery adding to an already large budget deficit, every dollar put toward an open-ended prize means one less for a grant or research contract. "I don't see how the pool is widened," says Molly Macauley of the nonprofit organization Resources for the Future in Washington, D.C. Some brilliant scientists might lose out if the government curtails or drops an existing research program, she notes.

Some legislators are also concerned about losing control over the purse strings if they allow an agency to craft an expansive prize program that may not be paid out for many years. For example, lawmakers are on the verge of significantly raising the current $250,000 cap on any one NASA prize, following a recommendation of a 2004 White House commission on space exploration. But Senate appropriators, pointing to the $12 million NASA has received for prizes, want additional details before handing over any more cash.

"With money still unspent, there's no point in putting more money there," says a Senate aide, "especially if the program has yet to be [better] defined." Although other research programs also give agencies some spending latitude, former NASA aide Lori Garver points out that "Congress doesn't like you giving money out outside the appropriations process." Funding more fundamental science with prizes could distort how academic scientists operate, says Neal Lane of Rice University in Houston, Texas, a former NSF director and science adviser to President Bill Clinton. Although DOE and NSF officials declined comment on the potential prizes they might offer, Lane says that goal-driven prizes could compel scientists to ignore truly odd findings if "the goal of the science [prize] is very narrow." Even if prizes are a small fraction of research funding, he says, the distraction could deprive society of a discovery more important than any prize officials could dream up. A spokesperson for Representative Frank Wolf (R–VA), who, as chair of the House spending panel that oversees NSF, inserted the prize language for the foundation into a budget bill, says that's not the legislator's intention. Any prize, the aide argues, would simply allow NSF to "push for more innovation" alongside its traditional grants.

But NSF's traditional academic clients may be left at the starting gate in any agency-sponsored competition if they can't afford the entry fee. "MIT doesn't give professors money to compete for prizes," says Jeffrey Hoffman, an applied space scientist at the Massachusetts Institute of Technology. Without start-up money, the average academic wouldn't have the flexibility to pursue new avenues of research.

To prize advocates, the possible pitfalls pale in comparison with the potential benefits. The X Prize showed what a challenge and a jackpot can do for any field, they say, not just space flight. The prize "has captured a lot of people's imagination," says Robert Simon, minority staff director for the Senate Energy and Natural Resources Committee. For NASA's Davidian, the competition "was a proof of concept"; supporters hope the idea will now take flight.

–ELI KINTISCH

Virology

Researchers Tie Deadly SARS Virus to Bats

Since its emergence in 2002, the origin of the SARS virus has proved elusive. Now two teams suggest that bats may be a natural reservoir

In the summer of 2003, two Australian researchers were pondering one of the mysteries of the deadly outbreak of severe acute respiratory syndrome (SARS): What animal had the virus come from? The new coronavirus had emerged in southern China in late 2002 and by the following June had killed 774 people, sickened more than 8000, and caused massive economic losses across Asia. An early finding of the SARS virus in masked palm civets sold at live animal markets proved a dead end when subsequent surveys failed to find the virus in either farmed or wild civets.

"If we have the money to survey only one species, which one should it be?" Lin-Fa Wang, a molecular biologist at the Australian Animal Health Laboratory in Geelong, recalls half-jokingly asking Hume Field, a veterinary epidemiologist with the Queensland, Australia, Department of Primary Industries and Fisheries in Moorooka. They placed their bet on bats. Both scientists had studied the Hendra and Nipah viruses, which ultimately proved to have bat reservoirs. They had also learned that bats, which the Chinese eat as well as use in traditional medicine, are among the live animals sold in markets in southern China, providing a plausible route of infection to civets.

Their hunch proved correct. Two groups have now independently identified bats as a natural reservoir of coronaviruses from which the SARS viruses that infected humans and civets likely emerged. Wang, Field, and colleagues at six institutions in Australia, China, and the United States describe their results in a paper published online by *Science* this week (www.sciencemag.org/cgi/content/abstract/1118391). Susanna Lau and colleagues at the University of Hong Kong (HKU) published their findings online 16 September in the *Proceedings of the National Academy of Sciences*.

Jam-packed. Close roosting, among other attributes, makes bats particularly well suited for incubating new diseases.

CREDIT: GETTY IMAGES

"This is indeed a huge discovery for SARS epidemiology and emergence, and it's nice to have it confirmed in two labs nearly at once," says Kathryn Holmes, a microbiologist who studies coronaviruses at the University of Colorado Health Sciences Center at Fitzsimons.

The identification of a SARS virus reservoir will enable animal and public health authorities to introduce countermeasures, which will likely center on minimizing contacts between bats and humans and livestock. It's also the first step in figuring out how likely SARS is to re-emerge among humans. Although the SARS-like viruses found in bats and civets are similar to the SARS virus that infected people, there are some important differences. This could mean that the human SARS outbreak was the result of a rare mutation and selection event difficult to repeat. Or it could mean that an intermediate host is needed to bridge the gap between a virus adapted to bats and one capable of infecting humans. Another possibility is that a virus more similar to the one that infected humans is already being harbored by different species of bats or other mammals. Finding SARS-like viruses in bats "opens a door," says Wang. "But there is still a lot to be done to provide enough data to assess the public health risk of a re-emergence of SARS," he adds.

The findings may have significance far beyond SARS. In just a little over a decade, viruses responsible for three deadly emerging diseases—Hendra, Nipah, and now SARS—have been traced to bats. Some suspect that bats may ultimately prove to be the reservoir for the Ebola and Marburg viruses, as well. Albert Osterhaus, a virologist at Erasmus University in Rotterdam, the Netherlands, says, "These findings indicate that we should give more attention to bats as sources of zoonotic infections."

Family relations

In their hunts for an animal SARS reservoir, the two groups followed similar methodologies in gathering and analyzing blood samples and fecal and throat swabs. The HKU group sampled monkeys, rodents, and several species of bats in the hinterlands of Hong Kong. Although other animals proved negative, they found a SARS-like virus in 39% of fecal swabs collected from Chinese horseshoe bats. About 80% of serum samples collected from the bats showed antibodies to the virus, an indication of a previous infection.

The team behind the *Science* paper went further afield, collecting samples from more than 400 bats representing nine species in several different bat genera and families from four far-flung provinces in southern, central, and northeastern China. The group also found large proportions of bats of three separate species within the Chinese horseshoe bat genus carrying antibodies to the SARS coronavirus. The group recovered five viral isolates from two of the same three horseshoe bat species and one species that did not produce any seropositive samples.

Partial sequencing of the viral isolates recovered by Li and his colleagues shows that they are all closely related but are still more genetically diverse than the coronavirus isolates recovered from humans and civets. That, along with the wide geographical distribution, high proportions of bats carrying antibodies, and genetic diversity, are all "what you would predict to see in a natural reservoir," says Wang.

Although scientists are now convinced that horseshoe bats are natural reservoirs of SARS-like coronaviruses, several unknowns make it difficult to determine the risk of SARS re-emerging in humans. For one, the bat SARS-like viruses and the human and civet SARS viruses differ significantly in the genomic regions that code for the receptors that bind to cells in the host. Holmes says this may indicate that these newly discovered viruses cannot easily jump the species barrier and infect humans. The differences in receptors may also explain why both groups failed to get the bat SARS-like viruses to grow in a cell culture that supported the growth of the human and civet SARS viruses.

But these are not reasons for complacency. Holmes notes that there could be additional animal reservoirs harboring viruses much closer to the one that caused the 2003 SARS outbreak. Christian Drosten, a virologist who studies the SARS virus at the Bernhard-Nocht Institute of Tropical Medicine in Hamburg, Germany, warns that new

Wide net. Jonathan Epstein and his colleagues collected samples from more than 400 bats from four widely dispersed provinces in China.

SARS-like viruses could possibly find some compatible receptors within a human body and then mutate to adapt to its new host. "Unexpected things can happen in a real infection situation," he says.

It is also not clear how the SARS virus got from the bat or another animal reservoir to humans. Both groups speculate that bats passed the virus to civets or other animals in the wild or, more likely, in the live animal markets of southern China where bats are sold as food. "In the markets, there are lots of species at high densities all mixed together with humans; this is a recipe for pathogens spilling over from one species to another," says Jonathan Epstein, a veterinary epidemiologist at Wildlife Trust's Consortium for Conservation Medicine in Palisades, New York, and a co-author of the *Science* paper.

Both groups are continuing to try to culture the viruses they isolated from bats. This would allow in vitro experiments to determine if the new viruses can infect human cells or if they must go through changes first. The teams would also like to infect animals with the viruses to see if they produce SARS symptoms. If they do, that would be further proof that these coronaviruses are closely related to the virus responsible for the SARS outbreak. Both groups also intend to continue to search for other animals and bat species that might be harboring SARS-like viruses.

Going batty

The SARS virus is just the latest—but by far the deadliest—scourge traced to bats. The Hendra virus, which is suspected of going from bats to horses and then to humans, caused two human deaths in outbreaks in 1994 and 1995 in Australia. The Nipah virus first surfaced among pigs and then spread to pig farmers and butchers in Malaysia and Singapore in 1998, eventually killing 108 out of 265 identified patients. The virus was traced to fruit bats feeding in orchards near or within pig farms. During the winters of 2001, 2002, and 2004, the Nipah virus apparently jumped directly from bats to humans, causing a number of fatal cases of encephalitis in Bangladesh. Nipah has also been found in bats in Cambodia.

Herwig Leirs, an evolutionary biologist at the University of Antwerp, Belgium, ticks off a long list of reasons why so many zoonotic diseases seem to originate in bats. To start, he notes that the genetic diversity of the more than 1000 species of bats creates numerous niches for viruses. Bats live from 5 to 50 years, which is much longer than most small mammals and "is useful for viruses seeking stable reservoirs," he says. Many species roost packed together in clusters, making it easy for a virus to spread through a colony. Cave-sharing among different species also facilitates transinfection across species, which in turn increases the chances of viral recombination. Finally, says Leirs, some bats can fly up to 20 kilometers a day foraging, and some species are migratory. "Bats have the capacity of widely transporting a pathogen over a relatively short period," he says.

Holmes suspects that there is yet another advantage helping make bats "magnificent vectors" for emerging diseases. She says bats seem to be able to carry and shed a virus for a long time without getting sick and without clearing the infection. Other scientists say this capability remains to be confirmed. Meanwhile, notes Field, degradation of bat habitats is pushing them out of their ecological niches and "giving them greater opportunity for contact with humans and livestock."

To keep these SARS-like viruses at bay, "we need to control contact between bats and humans and bats and other animals," says Shuyi Zhang, a zoologist at the Chinese Academy of Sciences' Institute of Zoology and a co-author of the *Science* paper. He notes that China's southern Guangdong Province banned sales of live civets in consumer markets in the wake of the SARS outbreak. Zhang is hopeful governmental authorities will now take similar steps regarding bats.

–DENNIS NORMILE

CREDIT: C. SMITH/CCM

Starting over. Scientific labs, stripped by looters in 2003, are struggling to recover.

In the Line of Fire

The question on everyone's mind at a recent meeting of scientists and sponsors was literally: How do we survive?

AMMAN—Wissam Al-Hashimi, a senior geologist with Iraq's Ministry of Oil and vice president of the Arab Geologists Association, was looking forward to coming to Jordan for a conference on Iraqi science. Then the grim reality of Baghdad intervened: Late last month, the British-educated scientist was kidnapped from his home and held for ransom. His daughter scraped up tens of thousands of dollars—and paid—but her father was not freed. The family finally tracked him down 2 weeks ago. "They found him in a morgue with two gunshot wounds in his head," says Moutaz Al-Dabbas, an environmental scientist at the University of Baghdad.

In Iraq these days, science often takes a back seat to survival. But the spiral of violence didn't stop several dozen Iraqi scientists from gathering here last week for a meeting* to showcase applied projects that can contribute to the country's reconstruction. One new initiative was unveiled: a virtual digital library of journals and other scientific materials sponsored by the U.S. State and Defense departments. And a fund of several hundred thousand dollars for peer-reviewed projects by skilled Iraqis is in the works. "Our purpose is to keep them doing science, not just sitting idle," says Abdalla Alnajjar, conference co-chair and president of the Arab Science and Technology Foundation (ASTF), a nonprofit organization based in Sharjah, United Arab Emirates. But to the frustration of attendees, no one stepped forward with more substantial funds for Iraqi R&D.

Survivor. Nahi Yousif Yaseen, director of the Iraqi Center for Cancer and Medical Genetics Research in Baghdad, heads a 72-person staff.

The corridors were filled with urgent questions, though—about how to help Iraqi researchers do science, and how to help them stay alive. At least 58 professors, 150 medical doctors, and dozens of scientists at institutes and ministries have been murdered since the Iraq war ended in April 2003, says Ahmed Moosa, an engineering professor at the University of Technology in Baghdad. Other Iraqi scientists corroborate his figures. "We feel there's a campaign to kill every scientist in Iraq," says Nahi Yousif Yaseen, director general of the Iraqi Center for Cancer and Medical Genetics Research in Baghdad. Hundreds more have been held for ransom.

Security is so poor that it prompted soul-searching at the meeting about whether grants that keep scientists in Iraq are even morally defensible. "I sometimes question the ethics of what we're doing," admits conference co-chair Arian Pregenzer, a senior scientist at Sandia National Laboratories in Albuquerque, New Mexico. Any grants for work in Iraq "are keeping scientists in a war zone," she says. "It's a terrible dilemma."

Death trap

The first shock hit Iraqi scientists after Saddam Hussein's fall, when an orgy of looting engulfed the country. Universities and research institutions were devastated. "They took everything," says Yaseen, who founded the country's only cancer research institute in 1995. The looters made off with refrigerators, furniture, and electrical fittings. "All we had left was a damaged building," he says.

Iraq's interim government in late 2003 gave Yaseen enough money to buy second-hand equipment and pay his 72 staff members. Since then, among other accomplishments, they've established three cancer cell lines, including one from brain cancer. "The only scientific research center that's working well now in Baghdad is ours," he boasts.

But it's not clear how long the cancer center will last. One staff member was murdered last year, and in recent weeks Yaseen has received a blunt warning: several envelopes with bullets inside. "Somehow they think we're helping the American army," he says. Four bodyguards protect him and escort his three children to school and university. Yaseen, who came to Jordan for the conference, says he calls home 10 or 12 times a day to check on his family. The stress is getting to be too much. He confesses that he is now looking for a job outside Iraq: "We have to leave—or we will face death."

All Iraqi scientists must watch their backs, but some appear to be more exposed than others. Mustansiriya University, with a campus in the heart of Baghdad, has been particularly hard hit. "Many professors have been killed there," says Al-Dabbas. Earlier this month "five of my professors applied for 1-year sabbaticals," says Ali Hassan Mahawish, dean of the College of Engineering at Mustansiriya. Last May, he says, a bomb on campus killed

CREDITS (TOP TO BOTTOM): ASSOCIATED PRESS

* The International Conference to Engage Iraq's Science and Technology Community in Developing Its Country, 18–20 September.

two students and maimed six others. Professors are growing wary of students elsewhere. At the University of Baghdad, many students have separated into Shia and Sunni cliques, says Al-Dabbas, who says it's potentially dangerous to appear to favor one group over the other. "If you give a low grade," he says, "you're frightened that they'll kill you."

To the rescue?

Efforts to engage Iraqi scientists in peaceful R&D began a couple of years ago. ASTF and Sandia's Cooperative Monitoring Center teamed up in August 2003 to seek out scientists, observe research facilities, and assess needs. Whereas the U.S. State Department at the time focused on weapons scientists, ASTF and Sandia embraced the whole research community. "We don't care where they used to work, what party they belong to," says Alnajjar. "We seek out scientific expertise on a merit basis." That impressed Iraqis. Until ASTF and Sandia came along, "we had no belief that anyone would come and help us. We were fed up," says Munther Naman Baker, an engineering professor at Mustansiriya University who later was appointed director of ASTF's Baghdad office.

After their reconnaissance, ASTF and Sandia ranked research priorities, matching the U.N.'s top three: public health, water quality, and the environment. "There is a meeting of minds," says Seifeldin Abbaro, officer-in-charge of the U.N. Development Group for Iraq, which funded a signature $11 million effort to restore the southern marshlands.

Next, ASTF and Sandia invited 20 Iraqis with promising ideas to a workshop in Amman last May where they worked with international collaborators to draft proposals for funding. That was a huge culture change, says Baker. Under the old regime, he says, "we did science on order of the state." The proposals that emerged included a DNA fingerprinting unit, screening for post-traumatic stress disorder, assessing potable water supplies, and combating desertification.

Applicants presented the finished proposals at last week's meeting in Amman. It's uncertain which ones will win funding. The U.K. government is considering bankrolling the DNA forensic science project, conceived by Ali Al-Zaag, dean of the Institute of Genetic Engineering and Biotechnology at the University of Baghdad, and Hanan Malkawi, vice dean of the Faculty of Science at Yarmouk University in Jordan. Other projects are still waiting. Some U.S. officials at the meeting spoke privately of a fund being pulled together from a variety of U.S. government agencies by the U.S. Civilian Research and Development Foundation. However, notes an official with the Arlington, Virginia–based nonprofit, "thousands of details need to be worked out."

One fully funded project was on display: the U.S. State Department's Iraqi Virtual Science Library (IVSL), a Web site (https://ivsl.org) with abstracts and full-text articles from thousands of journals, online course materials, and other information available free of charge to Iraqi scientists. Springer has donated access to its journals, and IVSL managers hope to acquire others at reduced rates. Sun Microsystems is donating eight servers and software, says a State Department official.

The $340,000 initiative, managed by the U.S. National Academies, will be tested this fall at seven universities in Iraq. "The idea is to connect scientists and engineers through the literature," says George Atkinson, science adviser to the U.S. secretary of state, whose office developed the project. At the outset, IVSL will be hosted on a Pentagon server. "We anticipate it being turned over completely to Iraq in the next few years," Atkinson says.

Fellowships will be on offer in another initiative that could allow 500 Iraqi researchers to spend up to 3 months abroad. Lab equipment and research materials, including textbooks, will be covered under the grants sponsored by Qatar, says Mohamed Djelid, director of UNESCO's Iraq office, which is managing the program. So far 48 researchers have been selected.

A job-placement initiative run by the State Department's Iraqi International Center for Science and Industry (IICSI) is making modest headway. Now in its second year, IICSI has placed 30 of 120 former weapons scientists on its rolls in jobs in Iraqi ministries. The initiative's new director, Edwin Kilbourne, a toxicologist and anthrax investigator formerly with the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, says IICSI will push harder to help former weapons scientists develop small businesses. It's a tricky proposition, he says: "They worry about whether their businesses are going to get blown up."

Managing IICSI has its challenges: Kilbourne can't visit the center, as it's located in a villa outside the so-called Green Zone that encompasses the U.S. Embassy compound. He can leave the Green Zone only with an armed escort, which would draw attention to IICSI—and make life more dangerous for scientists there.

One high-profile project involving former weapons researchers aims to learn whether the looting of the Tuwaitha Nuclear Research Center in April 2003 could pose a lingering health threat to the 100,000 people living in its vicinity. Some 200 barrels of "yellowcake"—uranium oxide—were stolen in the melee. Many were emptied and used for storing water or food, although 160 were recovered.

Last June, a team led by Iraq's Ministry of Science and Texas Tech University collected nearly 300 soil samples near Tuwaitha. They will be sent for analysis to the International Radioecology Laboratory in Slavutych, Ukraine, an outfit whose primary task is to monitor the environment around the destroyed Chornobyl nuclear reactor. (A U.S. agency is evaluating a request for funding the analysis.) Next, researchers will collect blood samples from people who may have been exposed to risky levels of radioactivity,

Academic citadel. The University of Baghdad, which suffered heavy losses after the invasion, is reportedly being divided into Sunni and Shia cliques.

CREDIT: ASSOCIATED PRESS

Profile: Jafar Dhia Jafar

AMMAN—He was Saddam Hussein's chief nuclear bomb maker, but he never managed to make a bomb. Now he's living in self-imposed exile in Dubai, United Arab Emirates, working as general manager of a company that's bidding for contracts to help rebuild Iraq. Jafar Dhia Jafar still commands respect from his peers despite the fact that he was a former key adviser to Saddam Hussein. That much was evident last week when they met him at a conference here on Iraqi science. The urbane 63-year-old high-energy physicist also impresses Western experts who worry that his knowledge of nuclear weaponry may appeal to Iran or other countries suspected of pursuing nuclear arsenals. "Jafar is one of the great senior statesmen of Iraqi science," says Alex Dehgan, who ran the Coalition Provisional Authority's program for former weapons scientists.

Jafar holds strong views on the reconstruction of postwar Iraq and the plight of his colleagues there, arguing that Iraqis must take the lead in restoring the nation's infrastructure (see main text). In a wide-ranging conversation with *Science*, Jafar revealed how close Iraq was to developing a nuclear bomb and discussed the future of science in his shattered homeland.

Jafar Dhia Jafar. Starting a third career.

The making of a weaponeer

Jafar grew up in Baghdad and attended university in the United Kingdom, where in 1965 received a Ph.D. in high-energy physics from the University of Birmingham. He was a member of the team that did the first experiments on NIMROD, a 7-GeV proton synchrotron at the Rutherford High Energy Laboratory in Oxfordshire.

He returned to Iraq in 1966 to take a position at the Iraqi Atomic Energy Commission. At the time the Soviets were building a 2-MW thermal research reactor at the Tuwaitha Nuclear Research Center for medical and basic science projects. Jafar headed the physics and reactor departments there but returned to Europe in July 1970 for a stint at Imperial College London and 5 years at the European laboratory for particle physics (CERN) near Geneva. David Websdale, a physicist at Imperial College London, worked with Jafar at CERN and recalls being impressed with a prototype detector for K+ mesons Jafar designed. Jafar was respected "as a talented physicist," says Websdale, who last had contact with him in the late 1970s. And Jafar was a "popular guest at bridge evenings."

A fateful invitation came in April 1975, when Saddam, then Iraq's vice president, recruited Jafar to return to Tuwaitha. Iraq had just embarked on a nuclear race with its longtime rival, Iran. In 1976, Iraq signed a $400 million deal with France and acquired among other facilities a research and testing reactor, Osirak, that ran on highly enriched uranium (HEU) fuel. Although the French managed the fueling of Osirak under International Atomic Energy Agency (IAEA) safeguards, experts pointed out that plutonium would be produced during normal operations and could be diverted for weapons use. Jafar insists, however, that "it was still a peaceful program."

In a brief period of calm, in 1977, Jafar attended a conference on nuclear science in Iran. It was clear then, as it is today, that Iran was intent on learning how to process uranium for fuel, Jafar says: "They wanted to have a complete fuel cycle." He says he has no special insights into whether Iran aims to develop a bomb, but he believes that an Islamic country in the Middle East has as much right to have nuclear weapons as Israel does.

Jafar's path veered in a new direction as it became intertwined with that of a young nuclear chemist, Hussain al-Shahristani, who had joined Tuwaitha in 1975 to work on neutron activation analysis. "We were good friends in the office but hardly saw each other outside the labs," says Jafar. "Shahristani is a devout Muslim, but I am not." In the turmoil that followed the 1979 revolution in Iran, Saddam, then president of Iraq, began rounding up and executing Shias.

Al-Shahristani was arrested in early December. "He was apolitical," Jafar says. "I thought for the first day or two it was all a mistake." Jafar wrote a letter to Saddam appealing for his release. There was no reply. In the meantime, he visited al-Sharistani's wife to try to reassure her; her home was being searched by security forces. Jafar became worried for his own family and decided to send his two sons to boarding school in England, where his British-born wife was receiving medical treatment.

A week or so later Jafar says he wrote another memo to Saddam about al-Shahristani, after which he was promptly arrested by the Mukhabarat intelligence service. "They probably thought I was preparing to leave the country." He was held for 20 months, although he was never tortured or even questioned, he says—unlike al-Shahristani, who Jafar later learned had been tortured from his first day of custody. With Saddam's human rights record at its most dismal in the early 1980s, Jafar says, "Shahristani is lucky that

including employees of the science ministry who helped corral the yellowcake barrels.

Still waiting

Despite months of preparation, the Jordan conference organizers were unable to draw serious funding offers, leaving scientists and organizers frustrated. Some U.S. officials say they are embarrassed by how little their own government is spending on Iraqi R&D and how little of that reaches Iraqis: The lion's share of the money for the IVSL library, for example, will be spent in the United States, and nearly 50% of IICSI's budget goes to security. Alnajjar, who has spent months trying to wring funds from wealthy Gulf nations, says he is "disappointed with the Arab countries." He also blames international organizations for a paralysis born from waiting for a "postconflict" calm. "You can't just sit and wait for this to happen," he says.

Others such as Jafar Dhia Jafar, who led Iraq's nuclear program under Saddam Hussein and now lives in Dubai (see sidebar, above), place the blame close to home. Jafar believes that Arab countries would respond if a plea came from the Iraqi government rather than from ASTF. If the government were to ask for assistance, Jafar believes that the Arab League would call a special meeting to discuss support for Iraqi scientists.

In the meantime, Pregenzer, an architect of the ASTF-Sandia initiative, says she and her colleagues are rethinking their strategy. One new emphasis, she says, will be to "get Iraqis more engaged in ongoing reconstruction efforts and other internationally funded projects in the Middle East." This could help those who are sticking it out as long as possible for the sake of the next generation, including the 3 million university students. "We don't want to leave them in the streets

CREDIT: R. STONE/*SCIENCE*

he wasn't executed." Al-Shahristani escaped from prison during the Gulf War in 1991 and is now deputy speaker of Iraq's new parliament.

Jafar was released in September 1981 and returned to Tuwaitha. Iraq was already at war with Iran, and in June, Israel had bombed Osirak. Jafar insists that the nuclear program adopted military objectives "as a reaction to the bombing," to build up Iraq's defenses. He says: "Many of us were convinced that without a military-oriented program, you couldn't have a peaceful nuclear program in the Middle East."

The French refused to rebuild Osirak. Jafar set out to enrich uranium without a reactor as a clandestine bomb effort got under way. An attempt to separate isotopes using gas diffusion sputtered, and experiments on isotope separation using lasers "came to nothing," he says, as Iraq could not build or buy sufficiently high-powered, tuned lasers. Jafar was told that equipment purchases could not raise a red flag. "We had to play with these conditions. It was difficult to develop a new technology completely on our own." But his lab-scale R&D on electromagnetic isotope separation succeeded in 1985.

The next phase was a pilot plant completed in 1987, after which Iraq started building production-scale units at the Tarmiyah site. Eight out of 140 were in place by the Gulf War, when the program had grown to 8000 people. "We were producing everything indigenously." Plans called for two new production units a month, with completion expected in 1992 or 1993. The units would perform optimally if low-enriched uranium were used; 4 tons of LEU would yield more than 100 kilograms of HEU per year, enough for several warheads. Bomb design started in 1988 and was proceeding in parallel, Jafar says, with a test anticipated by 1994.

"In the meantime," he says, "things happened"—such as the Gulf War, followed by intrusive U.N. inspections. The very first inspection team visited the Al Jazeera plant near Mosul, where "yellowcake"—uranium oxide—was processed into uranium dioxide, which in turn was converted into uranium tetrachloride, the feed material for electromagnetic isotope separation. "They deduced what was going on," Jafar says. "We declared everything, more or less, in July 1991. Saddam ordered the equipment destroyed by the Republican Guards. It was impossible to carry out any kind of program after that." Jafar insists that the program was not restarted after U.N. inspectors left Iraq in 1998.

That accords with the assessment of IAEA inspectors, who after conducting 237 inspections at 148 locations in the 3 months leading up to the 2003 war stated in an April 2003 report that they "did not find in Iraq any evidence of the revival of a nuclear program"—although they noted that they did not have the time to complete their review before the war began. Jafar scoffs at prewar claims that Iraq was still pursuing the bomb—including the discredited charge that it was trying to buy uranium ore from Niger. The United States and the United Kingdom, he claims, "had to concoct a nuclear threat."

Picking up the pieces

After the 1991 Gulf War, Jafar was enlisted as leader of a shock brigade overseeing Iraq's reconstruction. The first task was to rebuild the oil refineries. The director of the damaged Daura refinery said that the plant could be up and running by the end of 1992. He was asked to tap resources from throughout the oil ministry and from Petrochemical Project 3, the code name for the nuclear program. "A refinery is a piping job. We had 40 teams of welders, while the Daura plant had two," Jafar says. Within 2 months Daura was on line.

The speed and efficiency of the reconstruction in 1991 offers lessons for the current situation, says Jafar, who took charge of repairing the electricity sector. Before the Gulf War, Iraq had 9776 MW of installed capacity; in the wake of the war's aerial blitz, capacity stood at 750 MW, Jafar says. Through ingenuity and the ability to call upon an army of workers—thanks in part to the omnipresent threat of imprisonment for those who didn't follow orders—the national grid was back up by June at more than half prewar capacity. Jafar's successes pleased Saddam, who made him a personal adviser from August 1992 until the fall of the regime. Although Jafar last conducted his own research in the early 1980s, he kept active in the scientific community, serving as vice president of the Iraqi Academy of Sciences.

"Without a military-oriented program, you couldn't have a peaceful nuclear program in the Middle East."

—JAFAR DHIA JAFAR

Jafar fled Baghdad on 7 April 2003 during the Coalition invasion, crossing into Syria and going to Dubai. There, Jafar says he submitted to questioning by U.S. and U.K. intelligence agents. "My objective was to show them that they committed a grave mistake by invading Iraq under false pretences," he says.

He later co-founded Uruk Engineering Services, a Dubai firm that competes for reconstruction contracts in Iraq. Uruk has completed work on the refurbishment of a power station and is competing for a contract to develop the Zubair gas field in southern Iraq.

Although Jafar's current work is peaceful, nonproliferation experts say it's paramount that U.S. officials keep him on their radar screen. "The U.S. has a tremendous opportunity to obtain his input and benefit from his prestige," says Dehgan. "Perhaps even more compelling, the dangers of not engaging him may hold severe penalties for our regional security."

–R.S.

CREDIT: A. ABDEL NABY/REUTERS

Lingering risk. Researchers aim to study exposure to drums from the Tuwaitha nuclear center.

to be enticed by terrorists," says Moosa.

Some, however, may be better off getting out of the country. Moving scientists to a safe haven could give them "a chance to rejuvenate," Pregenzer says. "The goal is that they come back." One possibility, she says, is the new Middle East Consortium on Infectious Disease Surveillance. The public health and early-warning network could easily place a few Iraqis in Jordan or Egypt, Pregenzer says: "These sorts of things don't cost a lot of money." Jafar, speaking from personal experience, worries that such a strategy could backfire in the long run: "If scientists go out of the country, once they settle down it will be difficult to uproot them and send them back."

Iraqi scientists say it's a heart-wrenching decision to forsake their homeland. Baker, for one, is planning to leave Baghdad in the coming weeks to take a university position in Jordan. If it were his decision alone, he says, he might stay. But concerns for his family's safety trump patriotism. "Every day," he says, "is worse than the last." **–RICHARD STONE**

Random Samples

Edited by Constance Holden

Groovy Choppers

A Swedish anthropologist has found the first evidence of dental modification by early Europeans: Young men in Viking-age Scandinavia filed deep furrows into their upper front teeth.

Caroline Arcini of the National Heritage Board in Lund discovered the marks on the 1000-year-old skeletons of 24 young males, which were among several hundred skeletons unearthed from four different cemeteries in southern Sweden and held in storage in several museum collections.

Arcini thinks earlier researchers assumed the dental marks to be from wear or damage. But the furrows were clearly filed intentionally and with a great deal of skill, she reports in a paper in press at the *American Journal of Physical Anthropology*. She speculates that the men filled the grooves with a colored substance such as wax or fat mixed with pigment to make the marks more visible.

George Milner, an archaeologist at Pennsylvania State University, University Park, who has studied similar dental modifications in prehistoric North Americans, says such marks usually indicate a social group affiliation. These are surprising because "most instances of tooth modification have been found in Mesoamerica and South America." He says there have been occasional cases in Asia and Africa but none until now in Europe. Arcini says she hopes researchers will now be on the lookout for similar marks that might yield clues as to where the custom originated in Europe.

Italians Defend Darwin

Fearing that the teaching of evolution will disappear from Italy's elementary and middle schools, scientists last month organized a new group—the Society for Evolutionary Biology—to defend Darwin.

The new society was formed in reaction to the ministry of education's decision in 2004 to drop evolution from school curricula (*Science*, 30 April 2004, p. 677) in response to pressure from ruling conservative elements. Teachers and scientists mounted a protest, prompting the government to conduct an inquiry. The ministry withdrew its initial proposal earlier this year but has not made it clear how evolution will be reintroduced into classrooms.

The society's president, Giorgio Bertorelle of the University of Ferrara, says he aims to strengthen ties among evolutionary biologists worldwide and raise funds from Italian associations overseas. The furor in Italy could benefit science by raising public awareness about evolutionary biology, says Giorgio Bernardi, editor-in-chief of *Gene* and chair of the International Society of Molecular Evolution. Bernardi, one of hundreds of scientists who have joined the new society, predicts that in the end, "sanity will prevail."

Spider Essence in Amber

Even spiders have blood, although it is actually a bluish fluid called hemolymph. Now the oldest known droplets of spider blood have been discovered trapped in amber.

Paleontologist David Penney of the University of Manchester, U.K., spotted the droplets in a specimen, dated at 15 million to 20 million years old, belonging to the Museo del Ambar Dominicano in the Dominican Republic. He claims that the drops' preservation yields new information about how small organisms get trapped in amber.

It has been thought that insects become slowly engulfed after getting their feet stuck in resin. However, in the September issue of *Palaeontology*, Penney argues that because the droplets of spider blood were caught intact, the creature must have been submerged and had its legs broken very suddenly from a flow of liquid resin. Slow engulfment would allow the blood to dry out.

George Poinar of Oregon State University in Corvallis, an expert on amber-embedded fossils, agrees that "entrapment could have occurred quite rapidly." The museum specimen, he adds, shows that the "rapid and yet relatively gentle flow of amber resin can preserve rarely fossilized structures such as blood."

Penney suggests that such droplets may hold promise as an uncontaminated source of ancient DNA. Getting genetic material from bodily tissues is usually problematic because they may be contaminated by the DNA of internal microbes.

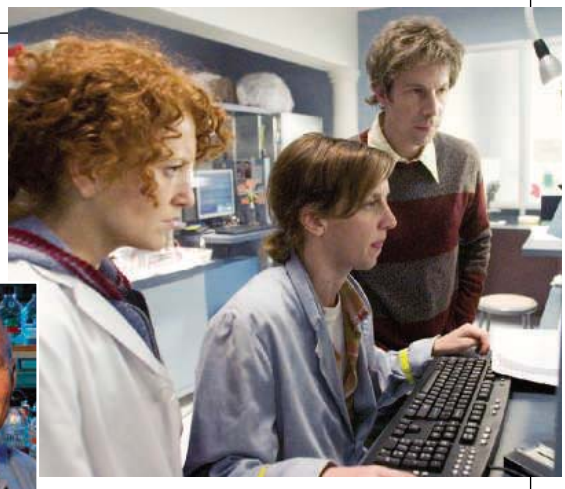
Blood and Steel

Heart of Steel (Hemoglobin), unveiled last week in Lake Oswego, Oregon, is one of a series of "protein sculptures" created by Julian Voss-Andreae, a quantum physics–trained German who is now an Oregon artist. The sculpture is made from tightly coiled steel tubing that trembles under the touch and which surrounds a red glass sphere.

CREDITS (TOP TO BOTTOM): ANNICA JEPPSON AND STAFFAN HYLL; DAVID PENNEY

Edited by Yudhijit Bhattacharjee

TWO CULTURES



Genetic action. Few researchers get the chance to share the richness of a life in science with a general audience. For medical geneticist Michael Hayden, that opportunity comes this week at the Vancouver International Film Festival in Canada with the debut of *The Score*.

The movie portrays a geneticist racing to isolate the gene for Huntington's disease, which she herself may be carrying. The concept for the story came from Hayden (inset), who studies the same disease at the University of British Columbia in Vancouver. (The gene was actually identified in 1993 by a research consortium organized by the Hereditary Disease Foundation.) The story was first enacted as a play by the Electric Company Theater in Vancouver and later adapted for the screen with the help of a $300,000 grant from Genome Canada. Hayden's lab worked closely with the filmmakers.

Apart from the inclusion of a risqué lab romance, Hayden is pleased with the result. The film focuses on the dilemmas of modern research, including the fierce competition between and within labs, the thorny relationship with pharmaceutical companies, and the ethical implications of integrating costly predictive genetic disease testing into the health care system. "It also portrays the vulnerability of science and the fact that it is not a cold, dry activity but rather tends to incite intense passions," says Hayden.

AWARDS

• A dozen scientists and engineers, and a lobsterer with a master's degree in biochemistry, are among the 25 winners of this year's MacArthur fellowships. Each awardee will receive $500,000.

• Ernest McCulloch and James Till, who together discovered the first stem cell, are the joint winners of this year's Lasker Award for Basic Medical Research. Edwin Southern, who developed a method for detecting specific genetic sequences among genomes, and Alec Jeffreys, who invented genetic fingerprinting, will share the Clinical Medical Research Award, and Nancy Brinker, who created the Susan G. Komen Breast Cancer Foundation, will receive the Mary Woodard Lasker Award for Public Service.

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RISING STARS

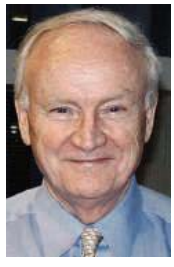
An open mind. A 37-year-old Canadian biologist has been tapped to head a new center to study the basic biology of stem cells at the University of Michigan (UM), Ann Arbor.

Sean Morrison, a native of Nova Scotia who came to Michigan in 1999, does research on the basic mechanisms that regulate stem cell biology, using blood-forming and nervous system cells as models. Harvard stem cell researcher George Daley calls Morrison, a Howard Hughes Medical Institute investigator, "a formidable force in stem cell biology."

Morrison says the $10.5 million center, to be based at UM's Life Sciences Institute, will hire up to seven researchers. "At this stage, many of the ideas we have about how stem cells will be used clinically will probably change rapidly over the next few years," he says. "If we focus on the basic biology and keep an open mind, we may ultimately have better results."

JOBS

Hanging it up. Seven years after becoming president of the Association of American Universities (AAU) in Washington, D.C., Nils Hasselmo has decided that he's old enough to retire. On 1 February 2006, 4 months shy of his 75th birthday, he'll step down from his job leading the consortium of 62 major research institutions.



Hasselmo, who moved to the United States from his native Sweden in 1956, trained as a linguist at Harvard University and served as president of the University of Minnesota, Twin Cities, before taking charge of AAU. His leadership has strengthened AAU's role in "higher education advocacy and policy development," says AAU chair Mark Wrighton.

Hasselmo says the country's most pressing need is "a clearly formulated national strategy to help the United States maintain its innovative capacity." And one step in that direction, he says, is for universities to find "new means of marketing their role in society."

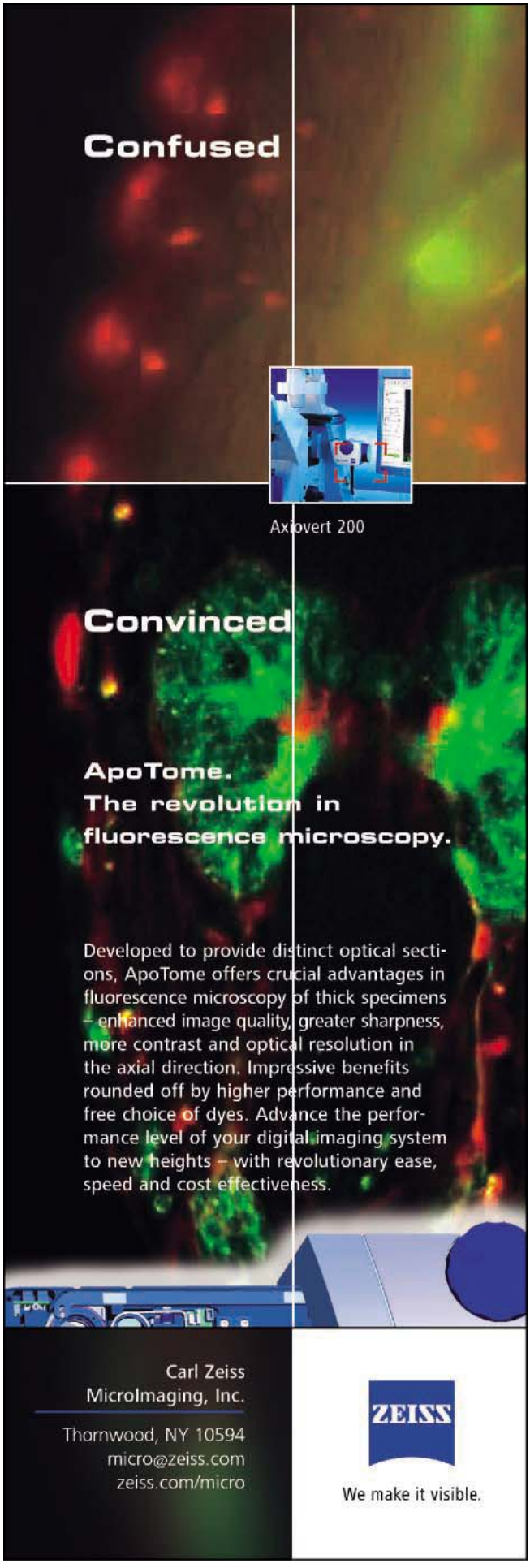
MISSING

Lost in ice. Two members of a five-person team from the Argentine Antarctic Institute have been missing since 17 September, after falling into a deep crevasse in the Antarctic ice.

The team, including biologist Augusto Thibaud and a member of the Argentine Navy, Teófilo González, was crossing the Collins Glacier by snowmobile en route to Argentina's Jubany Base on King George Island when it ventured into a zone of cracks that had been obscured by snow. The other team members managed to avoid the crevasse and were rescued from the danger zone the following morning by a Chilean helicopter.

A rescue effort, delayed 1 day because of a storm, has found no trace of the missing men, although there was faint hope of finding the men alive.

CREDITS (TOP TO BOTTOM): SCREEN SIREN PICTURES; INSET: MICHAEL HAYDEN; ASSOCIATION OF AMERICAN UNIVERSITIES; UNIVERSITY OF MICHIGAN



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World's Largest Flora Completed

CHINA IS HOME TO MORE THAN 31,000 species of vascular plants, more than any country except Brazil and Colombia. More than half of Chinese vascular plant species are found nowhere else, including many, such as *Ginkgo* and *Metasequoia*, which were once widespread around the Northern Hemisphere, but now survive only in China. Numerous noted botanical explorers and collectors from Europe, America, and China contributed valuable material to the herbaria of leading botanical institutions and greatly enriched the gardens of the world through their discoveries. The completion by Chinese botanists of the *Flora Republicae Popularis Sinicae* (FRPS), which outlines the characteristics of the country's huge flora, is an event of great significance; no flora of comparable size has ever been completed.

Rhododendrons in the Kama Valley, or Valley of the Flowers, east of Mount Everest in Tibet Autonomous Region, China.

CREDIT: GALEN ROWELL/CORBIS

This publication of this work was formally begun in 1958, but it was initiated in the 1930s by Hu Xiansu (better known as H. H. Hu) (*1*). Work on the flora virtually ceased during the chaotic "Proletarian Cultural Revolution" (1966–76). After 1978, Chinese botanists resumed and greatly accelerated their efforts, with major financial support from the National Natural Science Foundation of China, the Chinese Academy of Sciences, and the Ministry of Science and Technology. Finally, after 45 years of extraordinary effort by 312 Chinese botanists representing four generations, the Flora has been completed. It consists of 126 books, which constitute 80 volumes; it includes 31,141 species, 3407 genera, and 300 families of vascular plants. The final part was published in October 2004. The Flora includes all native and naturalized plant species, as well as China's economically important cultivated plants, such as crops, and plants that are grown in plantations. More than 20,000 species are illustrated in the 9000 odd plates of line drawings. FRPS is being entered into a database and will be made accessible through the Internet by the Institute of Botany, Chinese Academy of Sciences, Beijing.

Although FRPS provides an important step forward for the knowledge of Chinese plants, it is based on a relatively short period of study by the nation's botanists. Modern taxonomic research by Chinese botanists was not begun until 1916 (*1*), with earlier studies carried out mainly by European and American scientists. As a result, much of the important reference material is held by European and American institutions and was not always easily accessible to Chinese botanists, particularly during the "Cultural Revolution." The material that Chinese botanists have had available for study is mainly based on that assembled within China, most of it since 1949. Consequently, FRPS has certain deficiencies.

Because of these problems, an international collaborative project, the Flora of China project, was organized to produce a collaborative, revised English edition of FRPS. This project involves many Chinese and non-Chinese taxonomists from throughout the world and is supported by various funding agencies in China and the United States, including the National Natural Science Foundation of China, the Chinese Academy of Sciences, and the U.S. National Science Foundation, as well as the C.V. Starr, Kadoorie, and Stanley Smith foundations. Ten volumes of text and ten volumes of accompanying illustrations have been published to date (*2*). The project will ultimately result in the publication of 25 volumes of text and 25 volumes of illustrations and is expected to be completed by 2010.

By completing FRPS, Chinese botanists have made a great contribution to the understanding of the world's plants and have laid a more secure foundation for their conservation and sustainable use. Given the rapid development of China's economy and the consequent pressures on natural resources, this information is of vital importance. It is also hoped that the Flora may also present a useful model for botanists from other nations that are in the process of developing knowledge about their plant resources and encountering pressures similar to those felt in China.

QIN-ER YANG,[1] GUANGHUA ZHU,[2] DEYUAN HONG,[1] ZHENGYI WU,[3] PETER H. RAVEN[2]

[1]Laboratory of Systematic & Evolutionary Botany, Institute of Botany, Chinese Academy of Sciences, Beijing 100093, China. [2]Missouri Botanical Garden, St. Louis, MO 63166, USA. [3]Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China.

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1. W. J. Haas, *Arnoldia* **48**, 9 (1988).
2. The volumes are available online at http://flora.huh.harvard.edu/china/ and www.mobot.org/MOBOT/Research/asiaprojects.shtml.
3. We thank Xingguo Han, director of the Institute of Botany, Chinese Academy of Sciences, for his helpful discussion.

What Constitutes a Proper Description?

IN THEIR REPORT "THE HIGHLAND MANGABEY *Lophocebus kipunji*: a new species of African monkey" (20 May, p. 1161), T. Jones *et al.* attempt to describe a distinctive, new species of mangabey from Tanzania. The description of the new mangabey is based on two photographs, one of an adult male designated as the holotype, and one of unknown sex designated as a paratype. No voucher material was obtained, and the authors state, "The number of individuals in each of the two populations of this species is undoubtedly very small; no live individual should be collected at this time to serve as the holotype." Contrary to the statements in the published description, the photographs do not function as name-bearing types (*1*). Thus, *Lophocebus kipunji* Ehart, Butynski, Jones, and Davenport is not an available name and has no formal standing in zoology.

The photographs are not valid substitutes for a type specimen. The function of a type specimen in nomenclature is to provide an objective basis for the application of a species-group name. Jones and colleagues are encouraged to acquire a specimen, or part(s) thereof, and prepare a new description of this, as yet, undescribed species.

ROBERT M. TIMM,[1] ROB ROY RAMEY II,[2] AND THE NOMENCLATURE COMMITTEE OF THE AMERICAN SOCIETY OF MAMMALOGISTS

[1]Department of Ecology and Evolutionary Biology and Biodiversity Research Center, University of Kansas, Lawrence, KS 66045, USA. [2]Department of Zoology, Denver Museum of Nature and Science, 2001 Colorado Boulevard, Denver, CO 80205, USA.

Reference

1. International Commission on Zoological Nomenclature (ICZN), *International Code of Zoological Nomenclature* (ICZN, London, ed. 4, 1999). "Article 16.4. Species–group names: fixation of name-bearing types to be explicit. Every new specific and subspecific name published after 1999,... must be accompanied in the original publication[:] 16.4.1. by the explicit fixation of a holotype, or syntypes for the nominal taxon..., and, 16.4.2 where the holotypes or syntypes are extant specimens, by a statement of intent that they will be (or are) deposited in a collection and a statement indicating the name and location of that collection. (see Recommendation 16C)."

THE DISCOVERY OF A NEW SPECIES OF MONKEY is very important and heartening to preservationists everywhere ("The highland mangabey *Lophocebus kipunji*: a new species of African monkey," T. Jones *et al.*, Reports, 20 May, p. 1161). Unfortunately, as a taxonomic description, the Report leaves much to be desired and seems destined to sow confusion in future synonymies.

There are no hard and fast rules for the protocol of a species description, but certain features should be adhered to. It is usual to start with a brief taxonomic hierarchy, placing the new taxon in the set of animals; thus, Class, Order, Family, Genus, Species name (i.e., the proposed Linnaean binomial), "Sp. Nov.," "New Sp.," or some designation clearly marking the name as new.

"Ehardt *et al.*" give the citation for the new species as "Ehardt, Butynski, Jones and Davenport," that is, four of the seven authors of the paper. The purpose of the citation is to identify the paper, not to assign credit, and all of the authors should be cited.

This paper has not properly designated a type specimen. There is no provision under the *International Code of Zoological Nomenclature* (*1*) for designating a photograph as a type. The authors were understandably reluctant to collect a specimen of this rare species, but the proper course of action would have been to announce the discovery of the new species, publishing all of the excellent descriptive material and their quite convincing case for calling it new, without, however, naming it.

They have published a nomen nudum, a name that, because it is not backed by a type specimen, has no standing under the Code and that other taxonomic workers are free to ignore. Moreover, they rendered their name (*kipunji*) unavailable under the rules, meaning that not only is their entirely appropriate name, *Lophocebus kipunji*, not established, but that nobody can ever establish it.

STUART O. LANDRY

Professor Emeritus of Biology, State University of New York, Binghamton, NY 13902–6000, USA.

Reference

1. International Commission on Zoological Nomenclature (ICZN), *International Code of Zoological Nomenclature* (ICZN, London, ed. 4, 1999).

Response

LANDRY AND TIMM *ET AL.* SHOW A LAUDABLE concern about descriptions of new animal species that either are not, or appear not to be, compliant with the currently applicable *International Code of Zoological Nomenclature* (*1*). The aims of the Code, and of the Commission responsible for its periodic revision and implementation (ICZN), have always been to minimize chaos in animal nomenclature, hence ICZN's Mission Statement: "achieving stability and sense in the scientific naming of animals."

The destabilizing effect of publishing non–Code-compliant descriptions of new animal taxa is as old as the Code itself. Perhaps the most recent example is the invalid description of the fossil duck *Vegavis iaai* (*2*). Because no description for the generic name was provided, the binomial proposed for an extremely important

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fossil is invalid, or "unavailable" in the Code's terminology.

By contrast, Jones *et al.* undertook a series of consultations with the ICZN Secretariat and with several eminent taxonomists to ensure that their description of the highland mangabey *Lophocebus kipunji* was Code-compliant. Although under Article 16.4.2, it is stated that authors of new taxa must publish a statement of intent that extant types will be deposited in a collection, Article 73.1.4 provides an opportunity for the description of new taxa without the necessity of providing dead type specimens: "Designation of an illustration of a single specimen as a holotype is to be treated as designation of the specimen illustrated; the fact that the specimen no longer exists or cannot be traced does not of itself invalidate the designation." The Article, as formulated, thereby permits the description of threatened animals or those for whom the collection of specimens is otherwise impractical, impossible, or unethical. This situation has been dealt with in detail by Wakeham-Dawson *et al.* (*3*).

CREDIT: T. R. B. DAVENPORT

This photo, of an adult male highland mangabey *Lophocebus kipunji*, was designated by Jones *et al.* as the holotype.

The description of *L. kipunji* is also Code-compliant in all other respects, and the objections raised by Landry are unsupported. Although often the case, it is not required, nor always appropriate, that authorship of a publication describing a new taxon and its discovery be the same as the authorship of the name assigned under the Code. For *L. kipunji*, the authorship of the name (Ehardt, Butynski, Jones, and Davenport) specifically designates the authority assigning the name of the new species.

The allowance under the Code for designation of surviving specimens as holotypes needs to be more widely recognized, given contemporary concerns for the conservation of threatened species. There is no doubt that many newly described taxa will be threatened (*L. kipunji* will be designated as "critically endangered" in the IUCN Red List). Dead animal specimens should not be understood to be essential to the process of establishing new taxa. In such cases, supplementation with evidence such as sonograms and oscillograms of species-specific vocalizations, and molecular information (now readily derived from noninvasive samples, e.g., hair, urine, and feces) may contribute to validation. It should also be more widely recognized that establishing the taxonomic rank of new taxa and ensuring the availability of names are critical to the conservation listings (regional, national, and international) that assist in prioritizing, initiating, and supporting conservation efforts. Even the perception of the necessity for physical specimens under the Code could hamper and delay the very processes that determine whether newly discovered taxa survive.

The well-intentioned reactions of Landry and Timm *et al.* show that the current Code is open to different interpretations on the subject of type specimens (compare Articles 16.4.2 and 73.1.4 at www.iczn.org/iczn/index.jsp). The permissiveness of the Code in allowing illustrations of type specimens to make new

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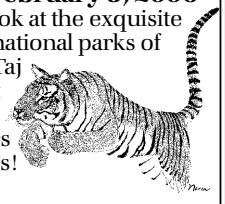

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names available, despite the subsequent loss or return to the wild of those types, is open to potential abuse. An obvious modest step forward would be to introduce a registration system for animal names. This would (i) alert zoologists to the appearance of newly described taxa and (ii) ensure that the names are Code-compliant and available.

Our comments support the preparation of a new edition of the Code—one that will prevent potential misinterpretations and perhaps encompass an open-access registration system. Such an effort, embracing the principle of bioinformatics, should unite all biologists involved in biodiversity conservation, systematics, evolutionary ecology, molecular biology, and related disciplines.

ANDREW POLASZEK,[1] PETER GRUBB,[2] COLIN GROVES,[3] CAROLYN L. EHARDT,[4] THOMAS M. BUTYNSKI[5]

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Quantifying Publication Impact

THE RANDOM SAMPLES ITEM "IMPACT FACTOR" (19 Aug., p. 1181) noted the proposal by Jorge Hirsch of the University of California, San Diego (*1*) that the total scientific output of a researcher can be judged by h, the largest number such that the researcher has at least h papers with h citations. Although this is indeed an indication of cumulative scientific impact, another measure, call it c, would also be interesting: the total number of papers from that researcher cited more than once by other research groups in the most recent calendar year. This alternative parameter c would be a much better measure of current research impact.

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

CORRECTIONS AND CLARIFICATIONS

News Focus: "A 'Robin Hood' declares war on lucrative U.S. patents" by E. Kintisch (26 Aug., p. 1319). The story incorrectly identified the name and scope of the organization Patients not Patents. The group focuses on drug patents.

Special Section on the Great Sumatra-Andaman Earthquake: Viewpoint: "A flying start, then a slow slip" by R. Bilham (20 May, p. 1126). The mention of the Richter scale in the second sentence of the second paragraph on page 1126 was incorrect. All magnitudes cited should be moment magnitude M_w, a scale that is defined by total energy release. The second sentence of the first paragraph on page 1126 incorrectly gave the energy equivalents of the earthquake. A magnitude of $M_w = 9.15$ corresponds to 3.35×10^{18} J, or 0.8 gigatons of TNT. This is equivalent to 11 days of total U.S. energy consumption, assuming a 2005 rate of 101×10^{15} British thermal units ($\approx 10^{20}$ J) (see www.eia.doe.gov/oiaf/aeo/index.html). However, although estimates of M_w range up to 9.3, the most reliable seismic energy release estimate is 1.1×10^{18} J, corresponding to ≈0.25 gigatons of TNT.

Reports: "Supramolecular assembly of amelogenin nanospheres into birefringent microribbons" by C. Du *et al.* (4 Mar., p. 1450). In this Report on amelogenin nanosphere assemblies and their tendency to form microribbon structures, the authors included a diffraction pattern that was attributed to these microribbons (Fig. 1F and Table S2). Elia Beniash (Forsyth Institute, Boston) subsequently informed the authors that the diffraction pattern and the d-spacings reported are analogous to those of cellulose fibers, and analysis of one of the microribbons by Beniash confirmed the presence of cellulose. The authors therefore conclude that the diffraction reported in Fig. 1F belongs to a cellulose contaminant fiber and not to an amelogenin microribbon. The authors have carried out new crystallization and characterization experiments of amelogenin birefringent microribbons that were free of contamination. The dimensions of the microribbons appear to be smaller than those indicated in the Report, with a wider distribution in length and width. The shape is not regular, although a ribbon-like morphology (similar to that of cellulose) is always preserved. These amelogenin microribbons, although birefringent, show either no or a very weak x-ray diffraction pattern. This suggests the presence of a preferential orientation in the nanosphere assembly, without any regular periodicity. The authors apologize for these errors and any inconvenience they may have caused.

HISTORY OF SCIENCE

Mapping the Roads to Current Science

John Tresch

Making Modern Science
A Historical Survey
by Peter J. Bowler and Iwan Rhys Morus

University of Chicago Press, Chicago, 2005. 537 pp. $65, £45.50. ISBN 0-226-06860-9. Paper, $25, £17.50. ISBN 0-226-06861-7.

It used to be easier to tell the history of science. Historians once focused on the "Scientific Revolution" of Copernicus, Galileo, Descartes, and Newton, showing how the discovery of the scientific method brought an end to the dogmas of theology and scholasticism. Later discoveries could be presented as the fulfillment of these first breakthroughs, with methods and concepts refined and applied to new fields by a series of geniuses leading up to the present. Things got more complicated with Thomas Kuhn's presentation of scientific revolutions in the plural, each with its distinct concepts, exemplars, and community of practitioners.

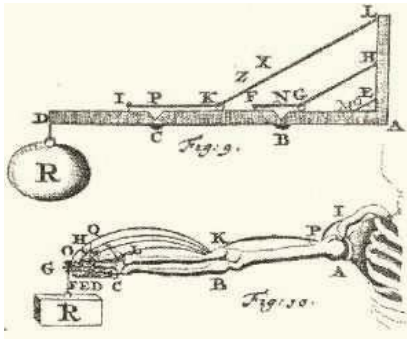
In the last 30 years, philosophically and sociologically informed scholars have, like Kuhn, broken the single history of science into multiple histories but have gone even further in questioning the role played by individual "great minds" and have put the very notion of scientific revolution in doubt. Historians now focus on the diverse methods developed in different subfields; the unpredictable but intimate interaction between theory and new technologies; and the influence of specific institutional, cultural, and political contexts on the creation of knowledge. The result has been the rise of microhistorical case studies, which revise familiar "textbook" histories of crucial experiments and revolutions yet never add up to a single big picture. It is telling that many of the texts that attracted discipline-wide attention in the 1990s—such as Bruno Latour's *We Have Never Been Modern* (*1*) and the volume *The Disunity of Science* edited by Peter Galison and David Stump (*2*)—were devoted to breaking down the idea of science as a single kind of activity. To tie together the detailed, local, highly particularized case studies of the new history of science into a single narrative seemed to be a goal that was not only difficult but theoretically backward.

With *Making Modern Science*, Peter Bowler and Iwan Morus have found a way to have their cake and eat it too. The book accomplishes the seemingly impossible task of introducing readers to what every student knows (or should) about modern science—the "textbook" histories of many of the most important developments in physics, biology, chemistry, and technology of the last 300 years—while at the same time using considerable historical and theoretical sophistication to bring out the complexities and ambiguities that undercut these myths. Lone geniuses are set within the research programs and the cultural concerns from which their discoveries emerged; "pure" theory is linked up to very concrete political, commercial, military, and even theological pursuits. What's more, the book shows that the history of science itself has a rich and varied history—how, for instance, in the 1870s and 1880s the idea of a longstanding "war between science and religion" was invented to bolster budgets in new research universities, and how in the 1920s and 1930s the treatment of the history of science as a history of ideas was designed to combat materialist, Marxist accounts.

Bowler and Morus (historians of science at, respectively, Queen's University, Belfast, and the University of Wales, Aberystwyth) divide the book into two parts. "Episodes" traces developments at key moments in specific fields as they began to take on a recognizably modern form, and the more theoretical "Themes" crosses periods and disciplines. The two parts can be fruitfully mixed and matched in various combinations. For instance, understanding of "The Scientific Revolution" of the 17th century can be deepened by juxtaposition with "Science and Gender"; the "Darwinian Revolution," with "Biology and Ideology"; and "Twentieth-Century Physics," with "Science and War."

As would be expected from the authors' previous publications, chapters on the life sciences (Bowler's primary field) and physics (Morus's specialty) are exceptionally strong; fields such as chemistry and the human sciences, often neglected in other overviews, are also given thorough treatments. The chapter "The Conservation of Energy" fills in the background of international discussions about the relations among imponderable fluids and convertible forces leading up to the consolidation of thermodynamics and is easily the best synthesis available on the topic. The chapter highlighting the institutions and research agendas that allowed the rise of vivisection and experimental biology in France and Germany also stands out. Furthermore, the book's treatments of scientific fields' changing social organizations, their relations with popular audiences, the forces that lead to their bifurcation or fusion, and their connections to various political and religious movements all put science firmly within the major currents of modern history.

Although the big names—Bacon, Joule, Mendel, Curie, *et al.*—are all present, the authors are particularly concerned with questioning the idea that a new scientific theory forms in the mind of one person and then goes out to transform the scientific world overnight. They show how continuities with previous theories and methods are often just as visible as discontinuities, while theories taken as foundational to a contemporary field were often interwoven with notions and goals we now see as beyond the limits of science (as with Newton's practice of alchemy or Lavoisier's concept of caloric). Bowler and Morus suggest that revolutions are often declared after the fact in order to clean up a much more tangled historical record as a way of providing a pedigree for present concerns. They recount, for instance, how Darwin's theory of natural selection was seen as outmoded by 1900 and only became revolutionary again with the work of population genetics and molecular biology decades later. Along similar lines, the book makes a strong case against simply dismissing as false theories like animal magnetism, the ether, or geological catastrophism. Such notions successfully explained certain phenomena and were enmeshed with deeply rooted concepts and practices—e.g., Joseph Priestley's enlightened



Early biomechanics. This figure from G. A. Borelli's *De motu animalium* (1680) reflects the idea that the human body could be understood as a mechanical system.

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use of phlogiston both to classify kinds of air and to guide progress by improving air quality in factories and working class districts. Further, the authors offer provocative insights on the limits and blind spots of current research programs. These include their observations on the limitations of genetic reductionism in biology and its tendency to neglect the interaction between organism and environment (which shapes the way in which genes are expressed) and their thoughtful reflections on the moral conflicts that arise from contemporary science's involvement in the military-industrial complex.

Attractively illustrated and easy to use, the book explains difficult scientific and philosophical issues in brief and often surprisingly clear terms. Because the authors generally describe formulas and proofs in words (to the amusing extreme of referring only to "the famous equation linking mass and energy" in a section on Einstein), even readers suffering from math phobia will feel at home. Each chapter is completed in a comfortable 20 to 30 pages and ends with an extremely well-chosen bibliography of general and specialized texts for those who wish to learn more.

Although the book explains techniques, theories, and concepts, it also offers rich histories of people and communities. The rivalries and reversals of fortune it relates through lively anecdotes and dramatic narratives underline the fact that science is in the first and last instance a human pursuit. Anyone exhausted by the science wars of the last decade, however, will appreciate the authors' thoughtful, naturalistic approach, which aims simply to present science as it has actually been practiced and understood. Bowler and Morus stress "a model of scientific development that accepts that [science] does indeed provide far more sophisticated knowledge of how the world works but refuses to see it as constructing a totally disinterested and immutably true model of nature." Their inclusion of social details does not entail sacrificing a recognition of the significance of conceptual advances, technical innovations, or successful research programs. Instead, they show us the indispensable background of training institutions, funding sources, and supportive cultural ideals that must be in place for scientific research to take the forms it has. Readers may find such a perspective particularly relevant in the current climate in the United States, where political and religious interests press for expanded control over research agendas.

The field of history of science has been calling out for a book just like this one. *Making Modern Science* will be a great help in introductory courses and will provide important background for advanced courses. In later editions—the book is likely to remain in print for many years—the authors may wish to expand their coverage of themes given understandably brief treatment here. Additional discussion of such topics as the relations between science and imperialism or the histories of mathematics, computing, and neuroscience would help balance the book's slightly disproportionate attention to the life and earth sciences and to the 19th century. Any gaps, however, are visible only because of the exceptionally broad and deep coverage the book already attains. Bowler and Morus's account will reward scientists who wish to see the history of their own field from a new and provocative perspective; students and teachers in need of a reliable introduction or a rapid brush-up; and readers with a general interest in the people, institutions, and concepts that have made science such a central aspect of the contemporary world. *Making Modern Science* is a timely, informative, challenging, and very welcome achievement.

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10.1126/science.1118059

HISTORY OF SCIENCE

An Old Approach to a Revolutionary Regime

J. B. Shank

Charles Coulston Gillispie is nothing if not an institution builder. In the 1950s, fresh out of graduate school, he pushed Princeton University into the avant garde of what was then a new and fairly exotic discipline: the history of science. There were few academic programs in the discipline when Gillispie moved to New Jersey, and through his initiative Princeton's became one of the earliest and most prestigious in the world. (Among its early faculty members was Thomas Kuhn.) Gillispie's *The Edge of Objectivity*, which appeared in 1960 (*1*), further helped to define the new history of science that programs like Princeton's began to teach. His other scholarship, especially on leading figures in 18th-century French science such as Sadi Carnot, Pierre Simon Laplace, and the aerial balloon pioneers Joseph and Étienne Montgolfier, did the same. Accordingly, Gillispie quickly established himself as a foundational figure in the new field of the history of science.

Even more monumental was the massive *Dictionary of Scientific Biography* (or *DSB*, as it affectionately came to be called by scholars) that he began to publish in 1970 (*2*). This indispensable reference work eventually ran to 16 volumes, and it was produced through the collaboration of dozens of scholars from around the globe. Gillispie served as the dictionary's editor in chief, and through the work's quality and success he created a lasting testimony to his own authority and esteem within the international community of historians of science.

Before the final volume of the *DSB* appeared, he had started a comparably monumental inquiry into the founding institutions of modern French science. *Science and Polity in France: The Revolutionary and Napoleonic Years* completes Gillispie's project, begun in the 1970s, to account for the simultaneous emergence of modern French politics and science between 1775 and 1815. It too is best described as an imperial scholarly edifice, for when placed alongside its equally erudite predecessor—*Science and Polity in France at the End of the Old Regime* (*3*)—it serves as a worthy capstone to Gillispie's 50 years of magisterial monument building within the history of science.

Science and Polity in France
The Revolutionary and Napoleonic Years
by Charles Coulston Gillispie
Princeton University Press, Princeton, NJ, 2004. 763 pp. $80, £52.95. ISBN 0-691-11541-9.

At a recent retrospective devoted to Gillispie's distinguished career, the octogenarian described the value of his and any other works of history as residing in "that which remains once the particular theses and arguments of a book have been forgotten." By this measure, *The Revolutionary and Napoleonic Years* is a fine book indeed. Gillispie's erudition is vast and his scholarship careful and authoritative, and accordingly the volume offers an unimpeachable empirical accounting of the transformations that French science experienced after 1789. The storming of the Bastille, the execution of Louis XVI, the rise of France's first-ever democratic polity, the new republic's subsequent descent into radical social engineering and terror, and the ensuing termination of republican rule by the strong-armed rationalism of the military dictator

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Napoleon Bonaparte: all this and more is present in Gillispie's book, where this political history is presented with a focus on its role in the emergence of modern French science. The invention and establishment of the metric system was one of the many outcomes of this political and scientific convergence, and Gillispie offers a full account of its history here. He also examines the end of the academy system of the ancien régime and its replacement by the new professional colleges and technical institutes that still anchor modern French science today.

The book is astonishingly comprehensive in its coverage. Were the author not such an engaging narrator, with a sly wit and an eye for interesting anecdotes, it would be easy to recommend *The Revolutionary and Napoleonic Years* as a kind of encyclopedia, one suitable for dipping into (aided by the comprehensive index) whenever knowledge about the many topics that it covers was sought. Gillispie, however, is an appealing storyteller, and thus those inclined to read his thick tome cover to cover will at least find their labors rewarded by readable prose and some compelling narrative drama. Nonetheless, the volume is anything but a narrative history, and accordingly scholars are much more likely to read the book selectively when researching particular questions, institutions, or personalities. Those who do will be no less rewarded because they will find a work that is broad and deep in equal measure, with a synoptic reach that would have overwhelmed a lesser scholar.

Taken together, the two volumes of *Science and Polity* aspire to be a kind of total history of French science and politics between 1775 and 1815, and the result will no doubt contribute greatly to scholarly work in this area for many decades to come. However, histories and encyclopedias are not the same thing. For those, such as myself, less inclined to look past the analytical agendas of scholars when evaluating their historical work, *Science and Polity* raises as many problems as it answers. Two decades ago, in a review of *Science and Polity in France at the End of the Old Regime*, Keith Baker criticized Gillispie's refusal to problematize the binary he assumed between "science" and "politics." Baker noted that science and politics are rarely (if ever) detached from one another and that the perspective that assumes their isolation is not a natural viewpoint but one produced historically through a contingent series of precise local developments. This transformation was of cardinal importance to the beginning of modernity, yet Gillispie avoided the challenge of explaining it historically by simply assuming the sui generis existence of an apolitical scientific sphere that only interacted with politics through external impacts. As a result, Baker argued, he ultimately effaced all the really important questions about how science and politics in fact became entangled in the historical co-production of scientific and political modernity after 1775 (*4*).

Before the Revolution. Jacques Louis David's 1788 portrait of the chemist Antoine Laurent Lavoisier with his wife and collaborator Marie Anne Paulze Lavoisier.

CREDIT: METROPOLITAN MUSEUM OF ART/JOSEPH MARTIN/THE ART ARCHIVE

Baker's criticism is just as appropriate to *The Revolutionary and Napoleonic Years*, and this fact is doubly frustrating when one considers what has transpired over the quarter century that separates the publication of the two volumes of *Science and Polity in France*. In fact, the years 1980 and 2004 (the volumes' publication dates) bookend fairly well the era of the "science wars," an overly bellicose label for what can more pacifistically be described as a period of thoroughgoing scholarly exploration of the relationship between science and politics. Few who encountered these debates (and no historian of science could have been oblivious to them) afterward maintained the same confidence about science's pristine status outside the temporal contingencies of political and social life. Not everyone became a radical social constructionist as a result of these discussions, but even those ultimately critical of constructivism at least came to recognize the powerful influence of politics in the making of much scientific knowledge. Consequently, between the extremes of radical constructivism on the one hand and apolitical scientific eternalism on the other, a vast middle ground was created where scholars judiciously, and often peacefully, struggled with the knotty relations between the allegedly universal character of scientific truth and the local and contingent structures that make science possible.

For those, like me, who occupy this middle ground, Gillispie's latest book is a disappointment. The work manifests no engagement whatsoever with the important discussions about science and politics that have occurred since 1980—save to dismiss them with a haughty silence. The author has also modified none of his binary and isolationist thinking about science and politics deployed in *End of the Old Regime*, despite the many trenchant criticisms of this conceptual framework that have been raised in the intervening years. Gillispie is, in short, a confident curmudgeon, one who remains blithely content with what he perceives to be the timeless epistemological bedrock of empirical positivism. If he is right that history books ultimately reduce to the sum total of their reliable empirical facts, then *Science and Polity in France* will indeed pass the test of time. But for those who believe that history is made outside the archive through careful and critical conceptual thinking about the meaning of historical facts, Gillispie's account of the simultaneous emergence of scientific and political modernity in France after 1789 will seem stubbornly and unproductively old fashioned. It will also contribute little to the important debates about the relationship between modern science and politics that are rightly at the center of contemporary science studies today.

As a meticulously accurate reservoir of archival material about a crucial moment in the making of modernity, *Science and Polity in France: The Revolutionary and Napoleonic Years* will no doubt teach scholars a great deal. But as an analysis of the convergence of science and politics in the historical making of modernity, the book offers little help to those trying to make sense of the important political and scientific currents still affecting modern world history today.

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10.1126/science.1115766

AIDS

Promote HIV Chemoprophylaxis Research, Don't Prevent It

Robert M. Grant,[1,2]* Susan Buchbinder,[2,3] Willard Cates Jr.,[4] Edith Clarke,[5] Thomas Coates,[6] Myron S. Cohen,[7] Martin Delaney,[8] Guiselly Flores,[9] Pedro Goicochea,[10] Gregg Gonsalves,[11] Mark Harrington,[12] Javier R. Lama,[10] Kathleen M. MacQueen,[4] John P. Moore,[13] Leigh Peterson,[4] Jorge Sanchez,[10] Melanie Thompson,[14] Mark A. Wainberg[15]

HIV infects more than 40 million people worldwide, and there are 14,000 new infections per day (*1*). No preventive vaccine is yet in sight (*2*). Even as available and proven prevention interventions are used, the HIV pandemic will not be stopped solely by talking to those at risk (*3*). Chemoprophylaxis with antiretroviral agents is a promising new approach (*4*). Clinical trials of daily oral antiretroviral dosing as preexposure prophylaxis (PrEP) have been initiated in Africa, Asia, and the United States and are planned in Latin America. Unfortunately, these trials have become controversial.

The first PrEP trials were set up to determine whether administration of tenofovir disoproxl fumarate (TDF) might safely protect high-risk, uninfected individuals from HIV infection. TDF has a long intracellular half-life, which allows once-daily dosing and the possibility of protection even if some doses are missed (*5*). The lack of drug interactions with hormonal contraceptives, tuberculosis therapy, or opiates makes TDF easier to use in those at highest risk. TDF-resistant strains are not generated easily.

TDF has an excellent safety record, with minimal effects on mitochondrial DNA polymerases that underlie some of the long-term toxicity observed with other antiretroviral drugs (*6*). The safety profile of TDF has been established in HIV-infected populations (*7*), and TDF was well tolerated in small-scale studies of uninfected persons (*8*). To confirm safety in diverse populations and to protect individual participants, monitoring of biomedical parameters is planned in all PrEP trials. The trials also involve frequent testing for HIV infection to allow the study drug to be stopped before there is a substantial chance of drug resistance occurring (*9*). Safety is of paramount importance for PrEP, because tolerability standards must be extremely high for any drug that is administered to uninfected individuals.

TDF can partially prevent infection of macaques by simian immunodeficiency virus (SIV) when administered at and after viral challenge (*10*, *11*, *12*). This effect may be overcome by repeated exposures to virus (*13*). Given the limitations of animal models, only clinical trials can determine the safety and efficacy of PrEP for humans.

Concerns about PrEP trials first came to international attention at the 2004 International AIDS Conference in Bangkok, when activists destroyed an exhibition booth of the drug developer that was donating drug and placebo for the trials (*14*). Shortly afterward, the Cambodian prime minister spoke against PrEP trials, and preparations for a trial in Cambodia were suspended (*15*). In February of 2005, the Cameroon government suspended administration of a study drug after a PrEP trial had full enrollment in that country. Reporting of these events and the underlying issues has been inconsistent and sometimes inaccurate, which contributed further to the controversy (*16*).

It is not the idea of PrEP itself, but how the research should be carried out, that is most controversial. How can participants be assured provision of the best preventive practices in a way that allows detection of additional protective effects by PrEP? Which populations are most appropriate for trials? How should community organizations be involved? How can treatment be provided during and after the trial, including treatment for HIV-1 infections that may occur? How should research populations be assured access to PrEP if it is shown to be useful? The importance of these issues was highlighted at a recent meeting organized by the International AIDS Society, which brought together sponsors, investigators, and community leaders from North and South to discuss solutions (*17*). There was a clear commitment to candid dialog that addresses these issues.

All participants receive standard prevention measures and are counseled that they should not feel protected by the "pill." The relevant research question is whether addition of daily oral TDF provides protection in addition to what can be achieved by known prevention strategies, including counseling, condoms (male and female), clean needles (*18*), and management of sexually transmitted diseases. Provision of these prevention measures is expected to decrease risk behavior during the trial (*19*) but has never eliminated it completely. The trials are designed to recruit large numbers of participants so that any additional protective benefit of PrEP can be discerned.

Investigators use several procedures to assure adequate counseling and to detect and remedy false optimism. Whether such "pill optimism" can be completely eliminated with counseling is being evaluated in PrEP trials, most directly in San Francisco and Atlanta. The risks of overoptimism are especially important if efficacy is modest or is promoted immodestly in communities. Alternatively, efficacy of PrEP may be high, which could empower a vision for an HIV/AIDS-free life and reinforce healthy behaviors. The challenges are not unique to PrEP and are inherent to HIV treatment programs and vaccine development.

Many prospective participants in Africa, Asia, and Latin America are especially vulnerable to HIV and a wide range of other harms, because they reside in some of the poorest parts of the planet, because they are women, or because their lack of legal status can lead to discrimination, extortion, summary judgment, or even execution. Community and governmental organizations often struggle with very limited resources and with international political forces beyond their control. Yet vulnerable populations are also those in most need of safe and effective ways to protect themselves from HIV infection, providing the ethical basis for studies in such groups.

Research in vulnerable populations is essential to evaluate the safety and efficacy of the intervention in those populations.

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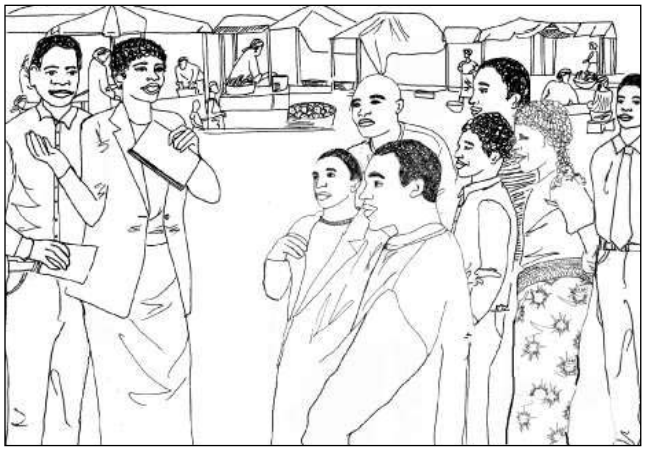
It cannot always be assumed that the outcome will be the same in different groups; efficacy may differ depending on the route of viral exposure owing to differences in transmission efficiency, drug penetration into tissues, or the types of cells that are first exposed to virus. Body size differs widely and directly affects drug levels that may impinge on efficacy and side effects. Other variables may be gender, genetics, adherence, gray and black markets for drugs, access to safe storage, and social circumstances. Performing prevention research only in Paris, San Francisco, or New York would be a tragic mistake that would perpetuate the situation of antiretroviral therapy, which has been optimized for the richest 2% of those infected.



A drawing depicting community discussions of PrEP research. This artwork is being considered for use in information booklets at the Malawi PrEP site.

ART BY DENISE TODLOSKI DESIGN/MALAWI PREP TEAM

Involvement of community members and leaders is a proven way to protect vulnerable persons who participate in research. Community advisory boards, community consultations, and independent, local, ethical review boards are well-established mechanisms for fostering community input into research design and implementation. They help to assure that studies provide benefit to study populations, while minimizing risks to individuals, and that there are procedures to obtain and maintain genuine informed consent. Community advisory boards and ethical review boards also address issues that emerge during the trial, including unexpected or serious adverse events, participant complaints, public misperceptions and rumors, and media communications. Access to ombudsmen for participants is warranted and is already provided by some ethical review boards. Local community advisers and ethical review boards should be involved in deliberations early in the development of research projects before sponsors' final approval is sought.

PrEP research was first proposed in 2001, before the advent of a global response for providing antiretroviral therapy (*4*). Some treatment advocates were angry that participants found to be HIV-infected before or during the trials might not have access to therapy and that antiretroviral drugs might be diverted from life-saving treatment programs. Since 2001, several agencies have been funding antiretroviral therapy on a massive scale. Clinics have opened, or are under development, at all PrEP trial sites, thereby providing access to antiretroviral therapy in these communities.

Community expectations for access to treatment should prompt good-will efforts but should not create ethical obligations that would block prevention research in locations where treatment is not yet available. The basis for collaboration between proponents of treatment and proponents of prevention research is clear: Successful prevention decreases the burden on treatment programs while sparing lives.

Research sponsors will need to ensure that medical care to treat adverse events related to the prevention study can be provided in poor countries. Financial mechanisms may have to be created. Comprehensive medical insurance that pays for treatment regardless of whether the injury was related to the study would increase total research costs manyfold and would be unfair to those not participating in research. Product liability insurance that covers injuries directly related to the study agent requires a process for judging the cause of the injury, which can involve legal systems that may not be accessible to study participants. A common approach of relying on academic medical centers and clinics to provide services to research participants requires that these centers be supported. Local solutions will frequently involve governments.

Concerns have been raised about whether PrEP will become available in poor countries (*17*). Access requires the support of international agencies such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which plans to evaluate results from current research. PrEP trials will obtain information about efficacy, safety, drug resistance, risk behavior, and immunological effects that bear directly on costs and benefits. High-quality research is needed as a platform for raising funds for access to PrEP, if it is proven to be useful.

Access also depends on drug prices. Gilead (the company that developed TDF) has established a global access program to allow it to become available at cost in 95 countries (*20*). Gilead has recently declared its intention to establish a nonexclusive licensing agreement with a drug manufacturer and distributor in South Africa (*21*). The decision not to seek intellectual property protection in Africa and parts of Asia makes it likelier that TDF will be widely available where it is most needed.

HIV PrEP research, as with all aspects of the fight against HIV/AIDS, is built on partnerships between sponsors, investigators, communities, and governments. Cooperation among such diverse interests is never easy, and coalitions are easily fractured by acts of disrespect, misinformation, or miscommunication. Such acts occurred too frequently in the early days of PrEP research, and hard lessons have been learned on all sides. While good-faith efforts are made to improve the conduct of trials, a balance must be struck between the necessity to conduct trials to very high standards and the need to find ways to prevent the spread of HIV infection.

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NEUROSCIENCE

Widespread Cortical Networks Underlie Memory and Attention

David Gaffan

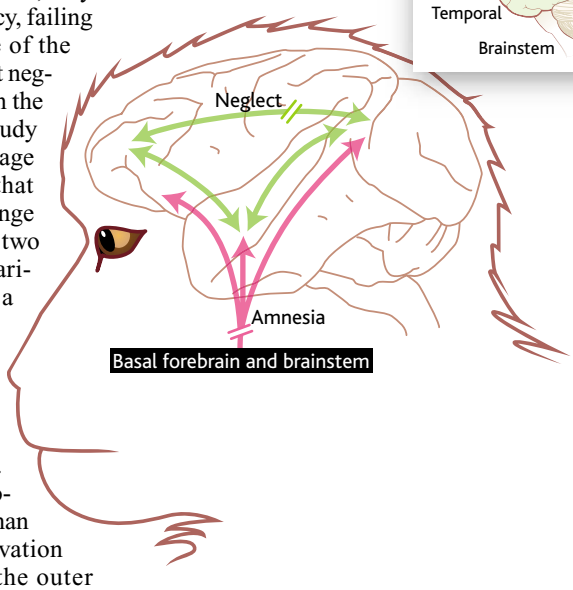
Circumscribed brain lesions can cause some profound but highly specific cognitive losses. One important example is anterograde amnesia, the inability to acquire new memories. This condition has been attributed to lesions in the temporal lobe, one of the major regions of the brain (see the figure). Another example is called neglect, the inability to sense, comprehend, and/or respond to stimuli on one side of space (the side opposite to that of the brain lesion). For instance, patients with left unilateral neglect will ignore all things on the left side of space and shift attention to the right side. If asked to bisect a line, they will do so with a rightward tendency, failing to even notice the left-hand side of the image. It has long been known that neglect is often produced by lesions in the parietal lobe of the brain. Now a study by Thiebaut de Schotten *et al*. on page 2226 of this issue (*1*) indicates that the phenomenon involves long-range functional connections between two brain regions—the frontal and parietal cortices—perhaps resolving a long-standing debate over the anatomical localization of the damage that produces this behavior. It also raises an interesting similarity with a recent proposed explanation for amnesia.

Thiebaut de Schotten *et al*. produced "temporary" neglect in human patients by brief electrical inactivation of the region that lies beneath the outer layer, or cortex, of the parietal lobe. Neuronal cell bodies constitute the cortical gray matter of the brain, whereas neuronal axons constitute the underlying white matter. This finding gives strong support to the idea that neglect results from the disruption of a widespread cortical network that involves neuronal cell bodies in large areas of cortex, including the frontal lobe, parietal lobe, and possibly the occipital lobe. This explanation of neglect, in terms of the white matter beneath the gray matter of the parietal cortex, stands in contrast to the traditional account of neglect that holds destruction of a specific set of neuronal cell bodies in the area of the lesion (the parietal cortex) accountable.

Naturally occurring lesions in the human brain usually involve both neuronal cell bodies in the cortex and subcortical axons. Experiments in monkeys, however, can investigate the cognitive effects of planned ablations that are specifically designed to leave white matter or gray matter intact. Ablation of large areas of the gray matter of the parietal cortex in the monkey, leaving the underlying white matter intact, does not result in neglect. However, neglect can be produced by cutting through the white matter, with only minimal damage to the gray matter (*2*). Evidence from the human brain reported by Thiebaut de Schotten *et al*. confirms that the cause of neglect is the same in the monkey and human brain.

Similarly, evidence for a white matter explanation of temporal lobe amnesia comes both from the human brain and from experiments with monkeys. Transection of the fornix, a subcortical white matter tract carrying axons to and from the medial temporal lobe, has quantitatively similar effects on memory in monkeys and in humans (*3*). A much more severe and dense amnesia than that produced by fornix transection is seen when other subcortical pathways, in addition to the fornix, are cut (*4*). These other pathways are damaged by naturally occurring lesions in the human brain only in conjunction with damage to medial temporal cortex itself. However, in the monkey, dense amnesia can be produced experimentally by a surgical procedure that sections the subcortical white matter pathways while leaving intact the medial temporal cortical areas [namely the hippocampus, the entorhinal and perirhinal cortex, and the parahippocampal gyrus (*4*)]. The crucial pathways that are interrupted in dense amnesia are thought to be the ascending axon projections from the basal forebrain and brainstem that pass through the anterior medial temporal lobe en route to widespread cortical targets (see the figure) (*5*, *6*).

The cognitive features of neglect and amnesia seem to be quite different from each other. However, recent evidence shows that neglect can be considered a failure to construct a representation of hemispace that is contralateral to the lesion, a representation that in normal function is based on memory retrieval just as much as on perception. Bisiach *et al*. (*7*) asked a left unilateral neglect patient to describe a familiar scene from memory, on two occasions from two opposite imagined viewpoints. The memory description omitted the left side of the scene as would be seen from whatever the current imagined viewpoint was. This is neglect in memory, with no input from current perception. Similarly, Hornak (*8*)



Long-range communications pathways in the brain facilitate attention and memory. Some long-range subcortical axonal pathways are illustrated on a lateral view of the left hemisphere of the macaque monkey cortex. Many ascending axonal pathways from the basal forebrain and brainstem (red) pass through a bottleneck in the anterior medial temporal lobe en route to their cortical targets. Cortical axonal pathways (green) pass through subcortical white matter to connect widespread areas of temporal, frontal, and parietal cortex. Interruptions to these long-range pathways (indicated by slashed lines) may underlie amnesia and neglect. (**Inset**) Lobes of the human cerebral cortex and cerebellum, as seen from the left side. The front of the brain is to the left.

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showed that a neglect patient's failure to explore the side of space contralateral to the lesion could be attributed to a failure to form and retrieve a representation of that side of space, rather than to any perceptual failure. Experiments with monkeys, in which one hemisphere of the brain was deprived of the visual information (although cortically completely intact) that would enable that hemisphere to form a representation of the contralateral side of space, gave further support to this representational account of neglect (*2*).

Neglect and amnesia are radically different clinical syndromes, and the point of this comparison is not to blur the distinction between them. Rather, the point is to suggest that widespread cortical networks spanning temporal, frontal, and parietal lobes subserve both memory and attention. The different clinical syndromes arise from different kinds of disruption to the long-range axonal communication among parts of the brain. This view contrasts with the traditional view of cortical localization of function, in which cognitive functions such as attention and memory are supposed to be subserved by spatially segregated areas of cortex. Understanding subcortical control of cortical plasticity in terms of widespread cortical networks, rather than assigning discrete parcels of cognitive function to discrete cortical areas, will enhance our current understanding of memory, learning, and other cognitive functions.

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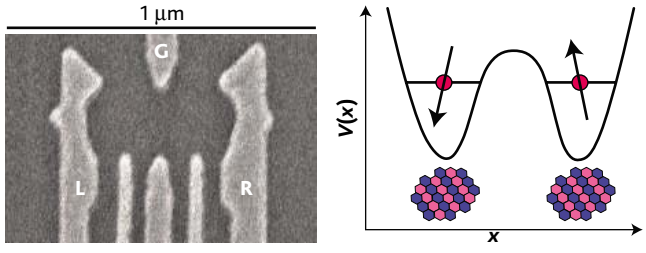
PHYSICS

Double Quantum Dot as a Quantum Bit

David P. DiVincenzo

Quantum dots, solid-state structures that are capable of confining a very small number of electrons, have long been thought of as artificial atoms. With the help of these dots, the tools of device engineering can be used to dissect new atomic physics phenomena. Important advances in recent years have made it routine in several labs to construct the smallest possible dots, each holding exactly one electron. One might expect this artificial "hydrogen" to have extremely simple electronic properties. In fact, because the host crystal is the semiconductor gallium arsenide, the quantum properties of this artificial atom are different from those of its natural analog in one striking respect: The single electron spin, rather than being coupled to the spin of one nuclear proton, is coupled to about a million spins carried by the gallium and arsenic nuclei. This bath of spins has previously been a nuisance, in the sense that it has obscured the quantum coherence of the bare electronic spin. On page 2180, Petta *et al*. (*1*) report that they have used a double quantum dot—in essence, an artificial H_2 molecule—to tame the effect of the nuclear spins. The results suggest novel ways in which the physics of these nuclear spins may be put to use in the search for a viable quantum computer.

As a result of years of steady improvement, the double-dot device (see the figure) of Petta *et al*. is a superb system for precise control of this artificial H_2 molecule. This is accomplished via the electric potentials of the six electrical leads shown. Overall variation of their potentials (with respect to a ground) sets the number of electrons in the two dots. The low-lying electronic states of the two-electron system, as with natural H_2, consist of a spin singlet (S) and three spin triplets (T), in which the two spin $^1/_2$ electrons combine to form either a state of spin quantum number 0 (S) or 1 (the Ts). The energies of these states are tuned in a variety of ways: There is an externally applied magnetic field that splits the triplets. The gate potential (G) controls the tunneling barrier between the two dots. Increasing tunneling increases the energy splitting between S and T, because of the Pauli principle—a singlet can lower its energy by (virtual) tunneling of one of the electrons to the other dot, forming a temporary polarized state; but this state is disallowed if the spin configuration is a triplet. One can also vary the degree of virtual tunneling in an unsymmetrical way, by applying a voltage between electrodes L and R. The virtual tunneling then is only in one direction, but the result is the same: control (in fact, much more reliable control) of the singlet-triplet splitting.



Dot SWAP. Double quantum dot device used by Petta *et al*. (*1*) to coherently manipulate electron spins. G is the gate electrode that controls the barrier between the dots. Voltages on the L and R electrodes control number of electrons in the left and right dots, respectively. Pulsing the potentials on these electrodes causes a SWAP of the spin states of the two dots. [Adapted from (*1*)]

This splitting arises from an effective spin-spin coupling that is very aptly named the exchange interaction in physics, because it does really correspond to an interchange of spin states: As a function of time, $|$up-down$\rangle$ is converted to $|$down-up$\rangle$, and back again. The computer science terminology for this operation is SWAP. SWAP is a very useful primitive for quantum computing (*2*), because it can be done partially, in superposition. In fact, the exchange interaction permits all transformations of the form (*3*) $|a,b\rangle \rightarrow \cos(\theta)\,|a,b\rangle + i\sin(\theta)\,|b,a\rangle$ to be done, for any value of θ, where θ is proportional to the interaction time. (This equation emphasizes that any pair of spin states a and b, pointing in any direction, get SWAPPED, not just the states $|$up$\rangle$ and $|$down$\rangle$.)

If this were the end of the story, the engineering of the quantum computer could be initiated immediately: It is well known how to use "fractional SWAP," either alone or in conjunction with other simple primitives, to implement a quantum algorithm. But nuclear spins, the state of which is not under external control in the device shown in the figure, make the story more complicated, and interesting.

Because each atomic nucleus in the GaAs crystal carries a nuclear spin (with angular momentum quantum number equal to $3/\hbar 2$), a simple calculation shows that the wave function of a single electron in one quantum dot has appreciable overlap with

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about $N = 10^6$ spin-3/2 nuclei. There are some subtle quantum-mechanical aspects to the interaction of the electron with these nuclei (*4*), but one obvious, large, essentially classical effect has been evident in several recent experiments: At any instant in time, each nuclear spin has a projection along the direction of the external magnetic field, adding or subtracting to the total effective field. The value of this Overhauser field can be enormous: If all Ga and As nuclei were maximally aligned with the external field, they would add about 5 T to it. The actual value in the experiment is much smaller, because the direction of each nuclear spin is essentially random (the temperature of the experiment, 100 mK, is "high" as far as the nuclei are concerned). But each dot has a random statistical excess or deficit of Overhauser field, which scales as $\sqrt{N}$, seen by the electrons as a ≈ 2-mT, slowly fluctuating field. These variations cause the observed decoherence time of the electron spin to be very short, about 10 ns.

Reenter SWAP, to erase the effect of this slowly fluctuating field, and greatly extend the coherence times of the two-spin states in the double-dot system. In the experiment, at time $t = 0$, the system can be set in the S state. But over time it acquires a random admixture of a triplet state T owing to the difference of Overhauser fields on the two dots. A SWAP is applied at $t = \tau$, interchanging the two spin states. When time 2τ has elapsed, each spin state has effectively spent an equal time in both dots, so that the average Overhauser field seen by both is the same. But S and T do not mix when the effective field is equal in the two dots. What is seen in practice is that, at time 2τ, the random admixture with T is completely undone, and the state becomes again pure S. There is a "singlet echo," in complete analogy to "spin echo" in magnetic resonance. This echo can be seen for 2τ exceeding 1 μs, proving that the actual spin coherence time is at least 100 times that of the originally observed value.

This experiment opens up the real prospect of using the two states, S and T, as a coded qubit, a possibility anticipated and thoroughly analyzed by Levy (*5*) some years ago. He showed that with a fixed magnetic field gradient between the two dots, the SWAP operation alone suffices to execute a quantum computation. The field gradient may itself be produced by differential Overhauser fields obtainable in these kinds of experiment (*6*, *7*). Again, there is a $\sqrt{N}$ fluctuation of these fields; but given the slowness of these fluctuations, there are more magnetic resonance tricks, like the spin echo, for using sequences of SWAPs to erase the effects of these fluctuations.

The remarkable thing about this experiment is that it can make use of all the tricks for reliable operations that are available in magnetic resonance, even though the controls are not magnetic at all—SWAP is controlled by a purely electric pulse. Real magnetic resonance manipulations of spins in this system would be orders of magnitude slower, and none of the results observed would have been possible. It appears now a real possibility that all-electrical control of spins in semiconductors may be a practicable route to real quantum computation.

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CHEMISTRY

New Gels for Mixing Immiscible Liquids

Philippe Poulin

Synthetic or natural porous media with a single continuous connected pore space are common. These materials are used in research laboratories as supports for catalysts, as well as in filters for automobile engines and coffee makers. But these classical solid porous media cannot be used to separate two different fluids, nor to keep two distinct liquids in contact for later separation. To achieve these aims, one needs a bicontinuous structure with two continuous media that are intimately combined but separated by porous walls. Such a novel compartmented structure could be of great interest for liquid purification and cleaning, for accurately enriching a liquid with another component dissolved in another liquid, for controlling chemical reactions between immiscible fluids, and for sorting the reaction products afterward. On page 2198 of this issue, Stratford *et al.* at the University of Edinburgh (*1*) report computer simulations of just such a material.

An ideal bicontinuous structure would be made of a rigid self-supporting scaffold with open and continuous walls so that gases, liquids, living cells, biomolecules, or particles can travel through the open spaces. But how can we make such a structure? Bicontinuous liquid phases do exist at thermal equilibrium (*2*). Some oil and water combinations can indeed form bicontinuous phases in the presence of surfactants in well-defined temperature and concentration ranges. Unfortunately, the intrinsic liquid nature and thermodynamically determined structures of these mixtures make the use of such phases for separation or filtration impossible.

Designing materials beyond thermal equilibrium could be a far more versatile way to create a variety of structures. For example, it has been shown that phase separations of fluids (*3*, *4*) can be used to create various structures including gels, droplets, and cellular systems. Fluid demixing thus seems to be an interesting approach to achieve complex morphologies. Consider a mixture of two fluids that are miscible at high temperature. By quenching the system at low temperature, the two fluids undergo phase separation. If the fractions of the two fluids are nearly equal, a bicontinuous structure forms. In the initial stages of the phase separation, the characteristic size (that is, the typical size of the separating domains) of the system is very small. It grows over time until a macroscopic phase separation occurs. If we perform such a simple experiment, we see a bicontinuous structure that spontaneously evolves with time.

At some point, when our ideal imaginary system reaches a characteristic size that would suit the bicontinuous material, we would like to stop the process and solidify the system right away. Unfortunately, the liquid system will just continue coarsening, driven by the unavoidable minimization of energy. Indeed, the growth of the characteristic size of the bicontinuous structure minimizes the amount of interface area between the two separating liquids. Because this interface costs a lot of energy, the characteristic size of the system keeps increasing. Stratford *et al.* (*1*) have proposed a very elegant approach to stop the coarsening at will. In numerical simulations, they have accomplished this by adding small particles that remain trapped at the interface between the two demixing

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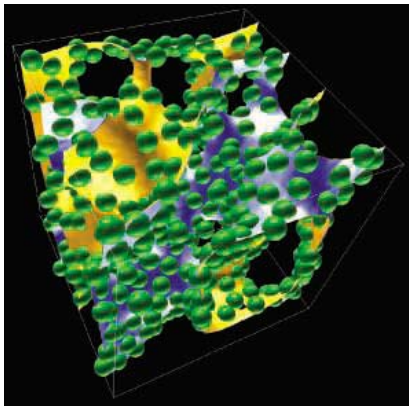
fluids. The wetting of the particles by the two phases is neutral, meaning that the particles exhibit the same affinity for the two fluids.

Under these conditions, the particles remain strongly and irreversibly stuck at the interface between the two fluids. In the initial stages of the phase separation, there is a large amount of interface area and the particles can freely move even if their motion is restricted in two dimensions at the interface between the fluids. Nothing prevents the coarsening from proceeding. But the particles become more and more concentrated as time elapses because the interface area is decreasing. At some point, the concentration of the particles confined at the interfaces is so high that the system becomes jammed. In other words, the particles cannot move anymore and they form a continuous self-supporting gel delimited by the interfaces between the fluids.

An important finding of Stratford *et al.* (*1*) is that the particles are not expelled from the walls. They can sustain a sufficient stress to preserve the walls and keep the three-dimensional gel intact. The authors call this new material a fluid bicontinuous particle-stabilized gel. In this state, the jamming of the particles has a dramatic consequence because the phase separation is suddenly arrested. The beauty of this new concept is the versatility and almost infinite tunability it allows. The system is no longer restricted to a single state imposed by thermal equilibrium and a solid structure can be achieved. Two critical challenges are solved in one shot. One can in principle use many kinds of organic or inorganic particles as long as they exhibit neutral or near-neutral wetting. By simply controlling the concentration of the particles, one can accurately select the characteristic size of the bicontinuous gel. The more particles added, the smaller the characteristic size of the compartmented media. If the gel is too weak to be directly used as a bicontinuous material for various applications, the particles can be fused or bound to each other via chemical reactions to make the material stiffer. Or subsequent additives can reinforce the walls. Because the system is frozen, a range of approaches to functionalize and adapt the system becomes possible. Also, even if the particles are jammed, there remains room between them so that two liquids in each continuous compartment can interact, chemically react, or exchange components through the pores of the walls. The size of these pores can be directly controlled by the size of the added particles. As a result, the liquids are in intimate contact with a huge amount of interface between them without being continuously mixed or emulsified.



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Gel jamming. Three-dimensional view of colloidal particles (green) trapped at the interface between two fluids during a phase separation. The liquids are not shown. The interface delimits two continuous media, which will ultimately form the pores of the bicontinuous gel.

This concept has been validated by Stratford *et al.* (*1*) using extensive computer simulations. Such simulations are extremely difficult because they must be undertaken on a large scale. But the efforts are worthwhile because the authors are presenting experimentalists with a particularly exciting challenge. Moreover, Stratford *et al*. provide an example of a potential application in the form of a unique simulation of cross-flow microfiltration.

The main difficulty for experimentalists will consist in finding particles and fluids to achieve neutral or near-neutral wetting conditions. However, this seems feasible. For example, Binks and colleagues at the University of Hull (*5*) have already shown that different kinds of emulsion droplets could be stabilized by controlling the wettability of particles at the interface between two fluids. By functionalizing mineral particles, Binks and his group have shown that the wetting of small particles by aqueous or oily fluids can be accurately controlled.

By combining experimental knowledge acquired in other studies (*3*–*5*), it is conceivable that the predictions of Stratford *et al.* will soon be validated on a laboratory bench. Clegg *et al*. (*6*) have been independently developing an experimental system that seems to be ideally suited for such an application. This system has been used to create emulsions, but small changes in the experimental conditions could lead to bicontinuous gels.

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CELL BIOLOGY

A Fungal Achilles' Heel

Joseph Heitman

The emergence of drug resistance in pathogenic microbes provides a resounding validation of Darwinian evolution and yet forces a sobering realization that we share this planet with organisms whose long-term survival threatens our own. This threat is particularly poignant with eukaryotic pathogenic microbes whose cellular machinery is similar to that of our own cells, making drug target identification and development of antimicrobial agents all the more challenging. And with the development of drug resistance in pathogenic fungi and parasites—such as resistance to azole drugs that target ergosterol (a unique membrane sterol in fungi such as *Candida albicans*) synthesis, or resistance to chloroquine and mefloquine in the malaria parasite *Plasmodium falciparum*—we are often only one step ahead of disaster. The study by Cowen and Lindquist on page 2185 of this issue begins with a basic interest in molecular events that presage microbial drug resistance (*1*) and unveils a role for a heat shock protein called Hsp90 in enabling pathogenic fungi to rapidly develop drug resistance. Hsp90 is best known as a molecular chaperone that allows cells and organisms to cope with protein folding defects that arise from insults including mutations and environmental stress. Cowen and Lindquist show that Hsp90 enables the evolution of phenotypic diversity in fungi in response to evolutionarily selective forces. The work also implicates Hsp90 as an Achilles' heel of pathogenic fungi that could be harnessed by small-molecule ligands to improve and extend the armamentarium of antimicrobial agents.

Enhanced online at www.sciencemag.org/cgi/content/full/309/5744/2175

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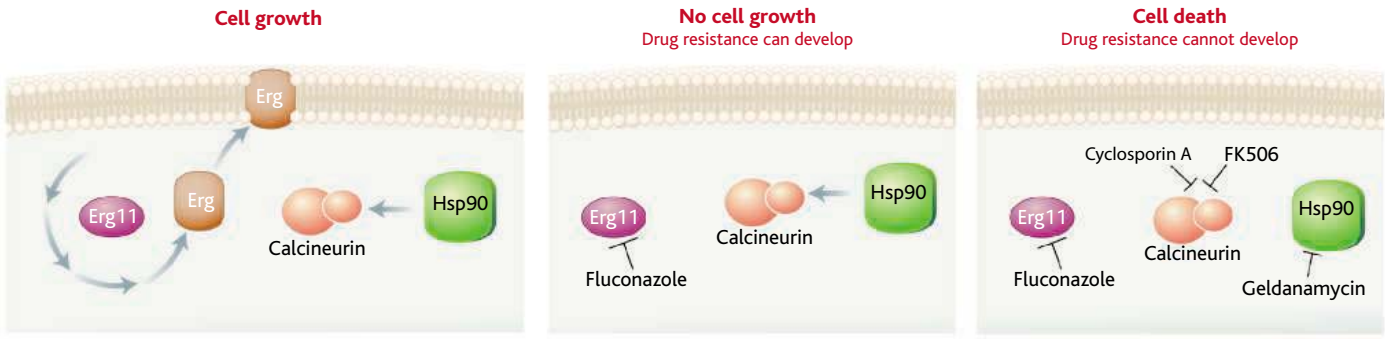
Resistance of fungi to antifungal agents can emerge by the overexpression of multidrug transporters that extrude toxic com-



Evolution of drug resistance in pathogenic fungi. Antimicrobial azole drugs (fluconazole) inhibit the activity of lanosterol 14-α-demethylase (Erg11) and block the production the membrane sterol ergosterol, inhibiting growth. Hsp90 and calcineurin are required for fungal cells to tolerate fluconazole, or to acquire and maintain drug resistance. Exposure to an Hsp90 inhibitor (geldanamycin) or calcineurin inhibitors (cyclosporin A or FK506) can enhance the effect of fluconazole, preclude or delay the onset of drug resistance, and reverse drug resistance.

pounds from the cell. The other alternative route is by molecular alterations of the ergosterol biosynthetic pathway or the homeostatic signaling pathways that impinge upon either ergosterol biosynthesis or cell survival when the biosynthetic pathway is limited (*2*). Ergosterol is required for cell proliferation. With the budding yeast *Saccharomyces cerevisiae* as their experimental palette, Cowen and Lindquist engineered isogenic yeast strains that express high or low levels of Hsp90 before and after either rapid or gradual selection for azole resistance. Their key finding is that Hsp90 is required both for the emergence of drug-resistant isolates in response to rapid selection and for continued drug resistance once it has occurred (*1*). These mutant isolates arise from alterations in the ergosterol biosynthetic pathway. In contrast, Hsp90 was not required for resistance mediated by the action of multidrug "pumps," which is acquired through a more gradual selection. Hsp90 is thus dispensable for drug resistance mediated by drug pumps but is essential for drug resistance mediated by the ergosterol biosynthetic pathway and signaling network mutants. Studies were extended to human fungal pathogens, including *Aspergillus terreus* and *C. albicans*, which frequently cause disease in immunocompetent and immunocompromised hosts.

Remarkably, Hsp90's function in drug resistance is exerted through calcineurin, a serine-threonine–specific protein phosphatase that is controlled by calcium and calmodulin, a calcium-binding protein. Calcineurin is the target of cyclosporin A and FK506, immunosuppressive drugs that revolutionized organ transplant therapy by inhibiting T cell activation (*3*). Calcineurin is essential for virulence of several pathogenic fungi including *C. albicans* and *Cryptococcus neoformans* (*4*–*8*) and also enables fungal cells to tolerate drugs that block ergosterol biosynthesis, even clinically derived resistant isolates (*8*, *9*). Cowen and Lindquist marshalled genetic and epistasis evidence to implicate calcineurin as a relevant target for Hsp90 action in promoting drug resistance. This model is supported by prior biochemical and drug combination studies that revealed a direct physical and mechanistic relationship between Hsp90 and calcineurin in mediating drug tolerance (*10*, *11*).

These discoveries have the potential to dramatically advance antimicrobial therapy. Azoles are fungistatic and not fungicidal, and therefore they inhibit the growth of fungal cells but do not kill them. Yet concomitant inhibition of either Hsp90 or calcineurin renders fluconazole and other drugs that target ergosterol biosynthesis fully lethal to fungal microbes (see the figure). This raises the prospect of developing potent drug combinations that enhance the intrinsic activity of drugs that target ergosterol biosynthesis while obviating (or at least reducing) the development of drug resistance. Small-molecule inhibitors and high-resolution x-ray crystal structures are known for both calcineurin and Hsp90 (*12*, *13*). Cyclosporin A and FK506 have been in clinical use for one to two decades, whereas the Hsp90 inhibitor geldanamycin is in clinical trials as a novel chemotherapy agent. Geldanamycin appears to be well tolerated in humans, which bodes well for additional clinical indications as a potential antimicrobial agent (*14*). A variety of active geldanamycin analogs have been synthesized, broadening the potential to identify molecules with improved antimicrobial spectra, reduced side effects, or oral bioavailability. Given a recent report that geldanamycin combined with cyclosporin A exerts a synergistic toxic activity against *P. falciparum* (*11*), this potential therapeutic regime might be applicable to fungi and parasites.

Beyond the specific implications for the evolution of drug resistance and applications to antimicrobial therapy, this study broadens our understanding of the myriad roles Hsp90 plays in generating cellular phenotypic diversity. Previous studies have shown that Hsp90 enables mutant proteins to maintain activity in a cellular context, and that it also serves as a capacitor that buffers the expression of phenotypic variation (*15*, *16*). The Cowen and Lindquist study extends this understanding to a third evolutionary paradigm: By maintaining a specific client protein (calcineurin), Hsp90 enables loss-of-function mutations in other genes to exert a phenotype (drug resistance) that otherwise would not be expressed. Thus, not only does the study by Cowen and Lindquist reveal a fundamental underlying principle by which a global cellular regulator, Hsp90, can govern adaptive evolutionary changes, it reveals specific contexts in which this insight can be brought to bear on important clinical problems. And gaining the upper hand on pathogenic fungi and parasites by thwarting the ability of Hsp90 to promote phenotypic diversity may be just the edge we have been searching for to tip the balance in our favor.

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edited by Edward W. Lempinen

SCIENCE EDUCATION

New Students, New Study Show Kinetic City's Expanding Impact

When blizzards and record snowfall threatened to paralyze the Boston area last winter, it would have been easy for kids to spend their Saturdays warm at home, watching TV. But at one Roxbury neighborhood center, the phones would ring with calls from worried kids or parents who hoped that their Kinetic City club would meet in spite of the weather.

For Adreenne Law Hampton, the center's youth director, their excitement was just one sign that AAAS's after-school science club was special. Now a new report offers further proof: Not only does Kinetic City improve science understanding in 2nd- through 5th-grade students, but it improves reading and writing skills, too.

Local Kinetic City organizers "knew they were getting a science program that children loved, that was interesting and entertaining and fun," said Shirley Malcom, head of Education and Human Resources at AAAS. "What they didn't know was that it also supported their reading and writing.…It's a matter of stealth learning."

As students return to school this fall, new clubs are opening in Texas, Tennessee, Florida, West Virginia, and Washington, D.C. More than 30 new clubs are set to open in Louisiana, most funded by the state's Department of Education, though the start could be delayed in the aftermath of Hurricane Katrina. In all, Kinetic City now counts about 130 clubs in 30 states and the District of Columbia.

Developed with major funding from the National Science Foundation's Informal Science Education Program, Kinetic City debuted in 1994 as a children's radio drama. Two years later it won a Peabody Award.

The old shows are still aired on satellite radio and some local stations, but Kinetic City today is geared more to informal after-school classroom settings and to the Internet. The guiding principle is that science, when taught through hands-on exercises, online games, creative writing, art, and physical education, is fun.

Students join the Super Crew—Keisha, Curtis, Megan, and Max—in a battle to save planet Vearth from a relentless virus known as Deep Delete. By teaming up to learn new science, they battle Deep Delete. The Kinetic City program has 16 missions, each with 2 weeks of activities, covering such subjects as planetary science, the human body, forces that shape the earth, and evolution.

The materials are based on the AAAS Project 2061 Benchmarks for Science Literacy. The clubs meet once or twice a week, after school or on Saturdays during the school year.

The report by EduMetrics, of Leesburg, Virginia, studied 92 children in Washington, D.C., schools. The students were required to read a challenging passage about the rainforest; then, pretending to be a creature who lived there, they had to write a letter to a desert-dwelling creature. The letter had to show that they understood the passage.

Before an 8-week engagement with Kinetic City, most of the children scored 0, and only two got top marks. Afterward, most completed the assignment satisfactorily and 28 children—30%—got top scores.

"That's a better outcome than you'll see in many programs expressly designed for reading and writing," said AAAS senior project director Bob Hirshon, who heads up Kinetic City. "They're going to carry that to other school assignments, and to other things they do in life."

Adreenne Law Hampton is excited to oversee Kinetic City again this fall at the Roxbury Multi-Service Center, part of the Timothy Smith Network for providing technology training to community residents.

"Last year," she said," after we had a Kinetic City project about the solar system, I heard students say: 'I'm going to be an astronaut!' 'I'm going to the moon!' It's good to hear them say that."

For more information, see www.kineticcity.com/.

AAAS GOVERNANCE

Annual Election

Ballots for the 2005 election of the AAAS president-elect, members of the Board of Directors and Committee on Nominations, and section officers were mailed to all active AAAS members as of the 9 September issue of *Science*.

Notice to members affected by Hurricane Katrina: Because the U.S. Postal Service is not delivering mail to areas with zip codes beginning with 395, 396, 700, 701, and 704, members in these areas must contact Linda McDaniel at Lmcdanie@aaas.org or by fax at (202) 371-9526 for a ballot.

Please return your marked ballot by 28 November. Ballots postmarked after that date will not be counted. If you do not receive a ballot by late October, contact Ms. McDaniel.

SCIENCE AND HEALTH

A Debut and an Award for "Healthy People" Project

With a new volume on biomedical research just about to launch, AAAS's Healthy People 2010 Library Initiative learned late last month that a 2004 booklet on asthma and allergies had been honored in the National Health Information Awards.

"Your Health: The Science Inside" is the sixth in a series of books published by the Healthy People project. Distributed for free through U.S. libraries, the books offer solid science insight to readers, particularly in low-income and minority communities.

The new booklet details the progress in biomedical research over the past 150 years—since the time before people understood that germs cause disease. It was designed to help readers think like scientists and take charge of their own health.

The Healthy People initiative began in 2000, funded by a $1.3-million Science Education Partnership Award from the National Center for Research Resources at the U.S. National Institutes of Health. Other volumes have covered HIV/AIDS, diabetes, high blood pressure, and other issues disproportionately affecting disadvantaged communities.

"Asthma and Allergies: The Science Inside" won the bronze award for a book in the patient education information class. The National Health Information Awards program, now in its 12th year, recognizes the best U.S. consumer health materials and programs.

For more information on the Healthy People project, see www.healthlit.org/.

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Extracellular DNA Plays a Key Role in Deep-Sea Ecosystem Functioning

Antonio Dell'Anno and Roberto Danovaro*

The regeneration of phosphates from the organic P pool is a key step in the regulation of P availability in the oceans (*1*). However, the reason why organic P is preferentially recycled in the deep ocean, where phosphates are not limiting, has yet to be clarified. This limits our understanding of the P cycle and ecosystem functioning on a global scale (*2*).

DNA is a P-rich molecule (10% weight to weight), but the role of DNA in P cycling has largely been ignored to date, as it is typically viewed only as the genetic material associated with living biomass (*3*). Here we provide evidence that DNA concentrations in deep-sea sediments worldwide are extremely high (0.31 ± 0.18 g of DNA m^{-2} in the top centimeter) (*4*) and that more than 90% of the DNA in these sediments is extracellular. We first estimated the extracellular DNA fraction by calculating the difference between total DNA and the DNA within living biomass, determined by synoptic determinations on virus, prokaryote, unicellular eukaryote (protozoan), and small metazoan (meiofauna) abundances. Another approach, conducted with a nuclease-based procedure that degrades only the extracellular DNA, supports this finding, revealing that 60 ± 4% of the total DNA pool is enzymatically digestible (*4*).

Additional polymerase chain reaction and dot blot analyses demonstrated that extracellular DNA estimates were not biased by the DNA released from living biomass during recovery (*4*). Our worldwide estimates indicate that the DNA content in the uppermost 10 cm of the deep-sea sediments is 0.50 ± 0.22 Gt. Therefore, extracellular DNA in deep-sea sediments (0.30 to 0.45 Gt) represents the largest reservoir of DNA in the world ocean. This amount is six- to eightfold higher than that of DNA contained in all benthic prokaryotes inhabiting the top 10 cm of the world marine sediments (*5*).

Pelagic-benthic coupling processes control the extracellular DNA distribution in world ocean sediments. This is suggested by the relationships between (i) DNA and phytopigment fluxes (Fig. 1A); (ii) DNA and phytopigment concentrations in surface sediments (Fig. 1B); and (iii) downward fluxes of DNA and sedimentary extracellular DNA content (Fig. 1C). The input of DNA from the photic layer to the deep sea stimulates the production of benthic prokaryotes, which represent ~90% of the total biomass (*6*). Our estimates indicate that the total DNA input to the sea floor is 1.26 ± 0.18 × 10^7 metric tons $year^{-1}$ and that extracellular DNA accounts for 13% of the total organic P flux (9.91 × 10^6 metric tons $year^{-1}$, below 1000 m in depth) (*7*) to the deep sea.

We calculated that the contribution of the P associated with extracellular DNA to the total organic P pool is ~3% (giving a global projection of 0.4 Gt of organic P) and that the residence time, in the top centimeter, is 40.3 years for organic P and 9.5 years for DNA. The measurements of high deoxyribonuclease activities (0.50 ± 0.15 mg of DNA m^{-2} day^{-1}) (*3*) provide more direct evidence that the extracellular DNA pool can substantially contribute to P cycling. The application of a diagenetic model allowed us to estimate that extracellular DNA remineralization in the top 10 cm of the sediment accounts for 17% of the total organic P regeneration (range, 14 to 21%) (*4*). All of these findings indicate that the extracellular DNA in deep-sea sediments is selectively remineralized within the organic P pool and rapidly degraded.

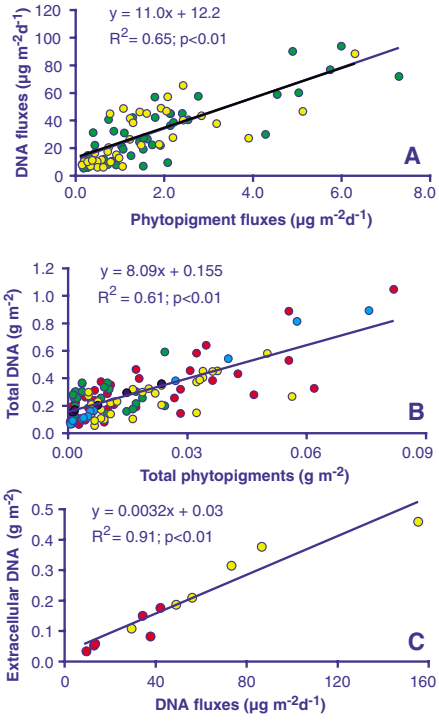

Fig. 1. (**A**) The relationship between DNA and phytopigment fluxes. Data are from the Atlantic Ocean at 3000 m and 4700 m in depth (green and yellow dots, respectively). d, day. (**B**) The relationship between total DNA and phytopigment content in the sediments. Data are from the Atlantic (red), Pacific (azure), Indian (green), and Southern (dark blue) oceans and the Mediterranean Sea (yellow). (**C**) The relationship between sedimentary extracellular DNA concentrations and DNA fluxes. Data are from the Atlantic Ocean (red) and the Eastern Mediterranean Sea (yellow).

Life in the deep-sea sediments is largely dominated by prokaryotes (*8*). Extracellular DNA, being a suitable C and N source (*4*), is important for deep-sea benthic prokaryote metabolism. Using synoptic measurements (*4*), we calculated that the use of extracellular DNA alone supplies 4, 7, and 47% of daily prokaryotic C, N, and P demand, respectively. Therefore, the use of a labile C and N source found in extracellular DNA results in fast P regeneration.

Our findings indicate that the availability of extracellular DNA can have profound implications on deep-sea ecosystem functioning, contributing substantially to P cycling and representing a key trophic resource.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/309/5744/2179/DC1
Materials and Methods
Figs. S1 to S3
Tables S1 to S3
References and Notes

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Coherent Manipulation of Coupled Electron Spins in Semiconductor Quantum Dots

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We demonstrated coherent control of a quantum two-level system based on two-electron spin states in a double quantum dot, allowing state preparation, coherent manipulation, and projective readout. These techniques are based on rapid electrical control of the exchange interaction. Separating and later recombining a singlet spin state provided a measurement of the spin dephasing time, T_2^*, of ~10 nanoseconds, limited by hyperfine interactions with the gallium arsenide host nuclei. Rabi oscillations of two-electron spin states were demonstrated, and spin-echo pulse sequences were used to suppress hyperfine-induced dephasing. Using these quantum control techniques, a coherence time for two-electron spin states exceeding 1 microsecond was observed.

Quantum coherence and entanglement have emerged as physical bases for information-processing schemes that use two-state quantum systems (quantum bits or qubits) to provide efficient computation and secure communication (*1*, *2*). Although quantum control of entanglement has been realized in isolated atomic systems, its extension to solid-state systems—motivated by the prospect of scalable device fabrication—remains a demanding experimental goal (*3*, *4*), particularly because of the stronger coupling of solid-state qubits to their environment. Understanding this coupling and learning how to control quantum systems in the solid state is a major challenge of modern condensed-matter physics (*5*, *6*).

An attractive candidate for a solid-state qubit is based on semiconductor quantum dots, which allow controlled coupling of one or more electrons, using rapidly switchable voltages applied to electrostatic gates (*7*–*9*). Recent experiments suggest that spin in quantum dots may be a particularly promising holder of quantum information, because the spin relaxation time (T_1) can approach tens of milliseconds (*10*–*13*). Although gallium arsenide (GaAs) is a demonstrated exceptional material for fabricating quantum dots, it has the potential drawback that confined electrons interact with on the order of 10^6 spin-3/2 nuclei through the hyperfine interaction. Here we present a quantum two-level system (logical qubit) based on two-electron spin states (*14*) and demonstrate coherent control of this system through the use of fast electrical control of the exchange interaction. We first show by direct time-domain measurements that the time-ensemble-averaged dephasing time (T_2^*) of this qubit is ~10 ns, limited by hyperfine interactions. We then demonstrate Rabi oscillations in the two-spin space (including a 180-ps $\sqrt{\text{SWAP}}$ operation between two electron spins) and implement spin-echo sequences, showing an extended spin coherence time, T_2, beyond 1 μs.

Isolating and measuring two electrons. Gate-defined double quantum dot devices are fabricated using a GaAs/AlGaAs heterostructure grown by molecular beam epitaxy with a two-dimensional electron gas 100 nm below the surface, with density ~2×10^{11} cm^{-2}. When biased with negative voltages, the patterned gates create a double-well potential (Fig. 1A). Tunnel barriers [controlled by voltages V_L and V_R (L, left; R, right)] connect each dot to adjacent reservoirs, allowing electrons to be transferred into the dots. Interdot tunneling (at a rate set by voltage V_T) allows electrons to be moved between dots when the detuning parameter $\varepsilon \propto V_R - V_L$ is adjusted. Measurements are performed in a dilution refrigerator with electron temperature T_e ~ 135 mK, determined from Coulomb blockade peak widths. Gates L and R are connected via low-temperature bias tees to high-bandwidth coaxial lines, allowing rapid (~1 ns) pulsing of these gates (*15*). High-frequency manipulation of a single electron, demonstrating the gigahertz bandwidth of this setup, was reported in (*16*).

Quantum point contact (QPC) sensors fabricated next to each dot serve as local electrometers (*17*, *18*), showing a few-percent reduction of conductance when a single charge is added to the adjacent dot. Figure 1B shows the conductance, g_s, of the right QPC sensor as a function of V_L and V_R near the two-electron regime. Each charge state gives a distinct value of g_s, decreasing each time an electron is added to the system or when an electron is transferred from the left dot to the right dot. Labels (m,n) in each region indicate the absolute number of electrons confined on the (left, right) dot in the ground state. We focus on transitions involving (0,2) and (1,1) two-electron states, where previous experiments have demonstrated spin-selective tunneling (*12*, *13*, *19*, *20*).

Voltage-controlled exchange. The relative energy detuning ε of the (0,2) and (1,1) charge states can be rapidly controlled by

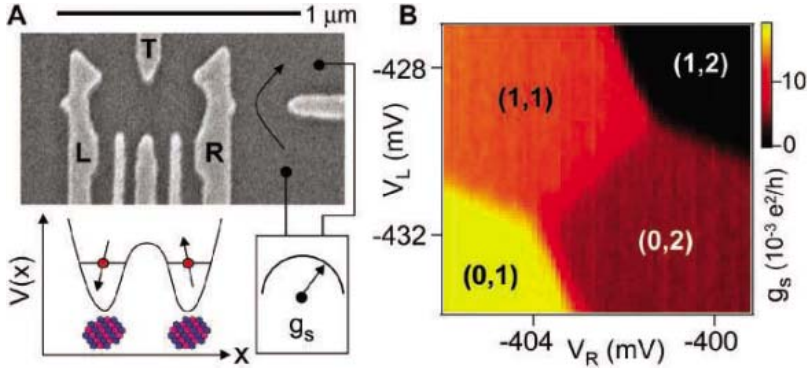

Fig. 1. (**A**) Scanning electron micrograph of a sample identical to the one measured, consisting of electrostatic gates on the surface of a two-dimensional electron gas. Voltages on gates L and R control the number of electrons in the left and right dots. Gate T is used to adjust the interdot tunnel coupling. The quantum point contact conductance g_s is sensitive primarily to the number of electrons in the right dot. (**B**) g_s measured as a function of V_L and V_R reflects the double-dot charge stability diagram (a background slope has been subtracted). Charge states are labeled (m,n), where m is the number of electrons in the left dot and n is the number of electrons in the right dot. Each charge state gives a distinct reading of g_s.

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applying calibrated voltage pulses to gates L and R (Fig. 2B). For $\varepsilon > 0$, the ground-state charge configuration is (0,2). Tight confinement in (0,2) favors a spin-singlet configuration, denoted (0,2)S. The corresponding (0,2) triplet states are energetically inaccessible, lying ~400 μeV above (0,2)S and are neglected in the following discussion. For $\varepsilon < 0$, the ground state configuration is (1,1). In this case, four spin states are accessible: the singlet (S = 0), denoted S [suppressing the (1,1) label]; and three triplets (S = 1), denoted T_-, T_0, and T_+, corresponding to $m_s = -1, 0, +1$.

In the absence of interdot tunneling, the two spins in the (1,1) configuration are independent; that is, S, T_0, T_+, and T_- are degenerate. At finite magnetic fields, S and T_0 are degenerate. When interdot tunneling is present, the (0,2) and (1,1) charge states hybridize, which results in an exchange splitting $J(\varepsilon)$ between the S and T_0 spin states of (1,1) that depends on detuning (Fig. 2B). Near zero detuning, exchange J ($\varepsilon \rightarrow 0$) becomes large (equal to half the splitting of symmetric and antisymmetric charge states at $\varepsilon = 0$); for large negative detuning, $\varepsilon \ll -J(0)$, exchange vanishes, $J(\varepsilon) \rightarrow 0$, and the spins again become independent. Except where noted, a perpendicular magnetic field B = 100 mT is used to split off the $T_\pm$ states from T_0 by the Zeeman energy $E_z = \pm g^*\mu_B B \sim 2.5$ μeV ($g^* = -0.44$ is the electron g factor in GaAs; μ_B is the Bohr magneton). The split-off T_+ state crosses the hybridized singlet S when $J(\varepsilon) = g^*\mu_B B$ (vertical green line in Fig. 2B), allowing $J(\varepsilon)$ to be readily measured, as discussed below.

In all measurements, a cyclical pulse sequence is used (see Fig. 2A for a schematic representation). A pulse transfers the (0,2)S state into the spatially separated (1,1) singlet state, S. The singlet state is manipulated with various control techniques (discussed below). After manipulation, the resulting (1,1) spin state is projected back onto (0,2)S for a measurement of the singlet probability P_S. P_S is measured with the QPC: the T states of (1,1) remain in a spin-blocked configuration, whereas the S state tunnels directly to (0,2)S. This spin-to-charge conversion readout is based on the same mechanism that results in rectification in dc transport found in similar devices (*19*, *20*). The majority of the duty cycle is spent in the measurement configuration ($\varepsilon > 0$), so that the slow (time-averaged) measurement of the QPC conductance reflects the charge configuration during the measurement phase (*12*, *13*).

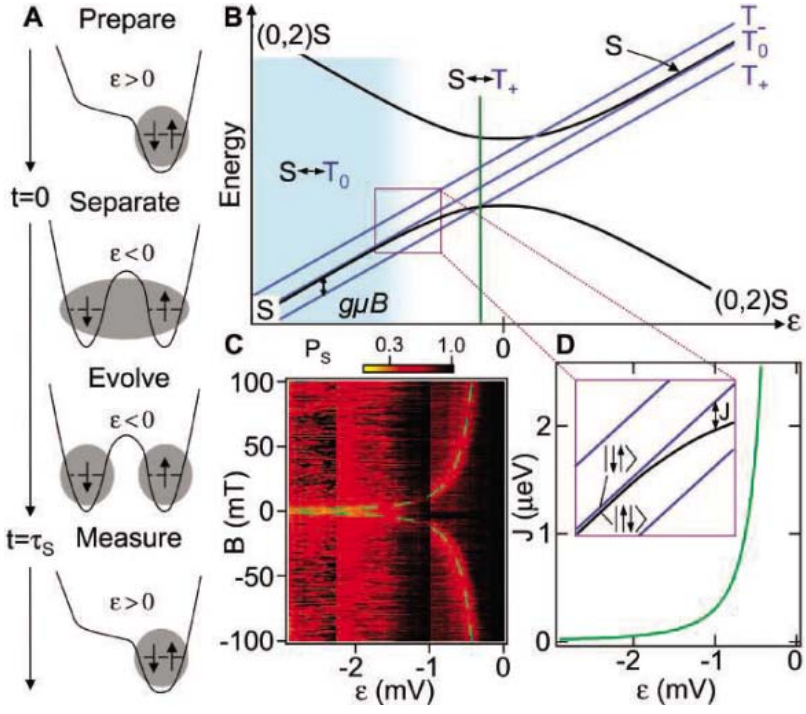

Fig. 2. (**A**) The control cycle for experiments generally consists of preparation, singlet separation, evolution of various kinds, and projection onto the (0,2) singlet state (measurement). Projective measurement is based on the spin-blockaded transition of T states onto (0,2)S, whereas S states proceed freely, allowing S to be distinguished from T by the charge sensor during the measurement step. (**B**) Energy diagram near the (1,1)-to-(0,2) charge transition. A magnetic field splits T states by the Zeeman energy. At the S-T_0 degeneracy (light blue region) and the S-T_+ degeneracy (green line), hyperfine fields drive evolution between S and the respective T states. (**C**) Singlet probability P_S after τ_s = 200 ns, as a function of detuning ε and magnetic field B maps out degeneracies of S-T_0 ($\varepsilon < \sim -1.2$ mV) and S-T_+ (dashed green curve). (**D**) Dependence of exchange on detuning, extracted from the fit of $J(\varepsilon) = g^*\mu_B B$ along the S-T_+ resonance, assuming $g^* = -0.44$ [dashed curve in (C)]. (Inset) For $J(\varepsilon) \gg g^*\mu_B B_{nuc}$, eigenstates S and T_0 are split by $J(\varepsilon)$. At large negative detuning, $J(\varepsilon) \ll g^*\mu_B B_{nuc}$, and S and T_0 are mixed by hyperfine fields but eigenstates $|\uparrow\downarrow\rangle$ and $|\downarrow\uparrow\rangle$ are not.

Even though we can coherently control and measure two-electron spin states electrically, the local solid-state environment remains critically important. For our device, each electron is coupled to roughly 10^6 GaAs nuclei through the hyperfine interaction. The hyperfine interaction results in an effective random magnetic field with magnitude $B_{nuc} \sim 1$ to 5 mT (*13*, *21*, *22*). These random hyperfine fields evolve slowly (>10 μs) relative to typical pulse sequence periods and result in spin dephasing, thereby coupling two-electron spin states (*23*–*28*). At large negative detuning, where $J(\varepsilon) < g^*\mu_B B_{nuc}$, these effective fields mix S and T states.

The logical qubit. With the $T_\pm$ states split off by an applied field $B \gg B_{nuc}$, the states S and T_0 form an effective two-level system (or qubit) with Hamiltonian

$$H = \begin{pmatrix} J(\varepsilon) & \Delta B^z_{nuc} \\ \Delta B^z_{nuc} & 0 \end{pmatrix}$$

where ΔB^z_{nuc} is the difference in random hyperfine fields along the applied field direction. To facilitate the following discussion, we define a Bloch sphere for the S-T_0 two-level system that has S and T_0 at the north and south poles (z axis) and the eigenstates of the instantaneous nuclear fields within this subspace, $|\uparrow\downarrow\rangle$ and $|\downarrow\uparrow\rangle$, as the poles along the x axis (Fig. 3A).

Dephasing of the separated singlet. The pulse sequence described in Fig. 3A is used to measure the dephasing of the separated singlet state as a function of the time τ_S that the system is held at large detuning [with $J(\varepsilon) < g^*\mu_B B_{nuc}$]. This time is a T_2^* time (the asterisk indicates an average over many experimental runs), because relative phase evolution of the separated spins can convert the initial singlet into a triplet, which will not be able to return to (0,2)S. The (0,2)S initial state is prepared each cycle by allowing tunneling to the reservoir with (0,2)S below the Fermi level of the leads and the (0,2) triplets above. This energetic configuration is held for 200 ns, and through a process in which an electron is exchanged with the leads, (0,2)S is prepared. The state is then separated into (1,1) using rapid adiabatic passage, where ε is swept from a positive value to a large negative value quickly (~1 ns) relative to the nuclear mixing time $\sim \hbar/(g^*\mu_B B_{nuc})$ but slowly as compared to the tunnel splitting of the hybridized charge states $\sim \hbar/J(0)$. This yields a separated singlet, S. After a separation time τ_S, the state is projected back onto (0,2)S, again using rapid adiabatic passage, and the system is held at the measurement point for a time $\tau_M \sim 5$ to 10 μs < T_1.

The average singlet probability measured after a separation time of 200 ns, $P_S(\varepsilon, B, \tau_S$ = 200 ns), is shown in Fig. 2C as a function of

detuning at the separation point and applied field (*29*). Evident in the data are a funnel-shaped feature where S and T_+ cross (vertical green line in Fig. 2B) and are rapidly mixed by hyperfine fields. The degeneracy occurs at $J(\varepsilon) = g^*\mu_B B$, allowing $J(\varepsilon)$ to be measured (Fig. 2D) by mapping the location of this feature in $P_S(\varepsilon,B)$. At larger detuning, where $J(\varepsilon) < g^*\mu_B B_{nuc}$, the S and T_0 states approach degeneracy and are susceptible to hyperfine mixing, which reduces P_S (light blue area of Fig. 2B). When $B < B_{nuc}$, all three degenerate triplet states can mix with S at large detuning, which further reduces P_S as compared to the finite-field case.

For applications involving the manipulation of entangled pairs of electrons, a relevant question is how long the electrons can be spatially separated before losing phase coherence. We measure this time by varying the singlet separation time τ_S. The time evolution of the average singlet return probability, $P_S(\tau_S)$, measured using the pulse sequence in Fig. 3A with $\varepsilon = -6$ mV, is shown in Fig. 3B. As τ_S increases, P_S decreases from ~1 on a 10-ns time scale, saturating after 20 ns to $P_S \sim 0.5$ (0.7) for $B = 0$ (100) mT.

A semiclassical model of dephasing of the separated singlet was investigated in (*23*). It assumes independent quasistatic nuclear fields acting on the two spins (*26*, *30*) and ideal measurement contrast, and yields Gaussian-like decay on a time scale T_2^* from $P_S(\tau_S = 0) = 1$ to long-time saturating values $P_S(\tau_S \gg T_2^*) = 1/3$ for $B \ll B_{nuc}$ and $P_S(\tau_S \gg T_2^*) = 1/2$ at $B \gg B_{nuc}$. The field dependence is caused by the lifting of the triplet degeneracy with the external field, although the naïve expectation based on incoherent mixing would be $P_S(\tau_S \gg T_2^*) = 1/4$, not 1/3, at $B = 0$. Fits to the measured $P_S(\tau_S)$ yield $T_2^* = 10 \pm 1$ ns, corresponding to $B_{nuc} = 2.3$ mT, consistent with previous measurements (*13*, *22*, *31*). An observed ~40% reduction of contrast is treated as a fit parameter. The predicted weak overshoot of P_S for $B = 0$, a remnant of Rabi oscillations (*23*), is not seen in these data.

Spin SWAP and Rabi oscillations in the $|\uparrow\downarrow\rangle$, $|\downarrow\uparrow\rangle$ basis. By initializing from (0,2)S using slow ramping of detuning, the (1,1) system can be initialized into the ground state of the nuclear field [defined as $|\uparrow\downarrow\rangle$ (Fig. 2D, inset)] instead of the singlet state S. This initialization scheme is illustrated in Fig. 4A: after preparing (0,2)S (as described above), detuning is swept to $\varepsilon < 0$ slowly relative to tunnel splitting but quickly relative to the nuclear mixing time through the S-T_+ degeneracy. The system is then ramped slowly as compared to the nuclear mixing time ($\tau_A \sim 1\ \mu s \gg T_2^*$) to large negative detuning. This slow lowering of $J(\varepsilon)$ leads to adiabatic following of the initial state S into the state $|\uparrow\downarrow\rangle$, the ground state of the Hamiltonian with $J \rightarrow 0$ (*30*, *32*). Readout follows the same steps in reverse: ramping slowly out of the large detuning region unloads $|\uparrow\downarrow\rangle$ to S and $|\downarrow\uparrow\rangle$ to T_0. Then, moving quickly though S-T_+ degeneracy and finally projecting onto (0,2)S measures the fraction that was in the state $|\uparrow\downarrow\rangle$ before readout.

Once initialized in $|\uparrow\downarrow\rangle$, the application of a finite exchange $J(\varepsilon)$ for a time τ_E rotates the spin state about the z axis of the Bloch sphere, in the plane containing $|\uparrow\downarrow\rangle$ and $|\downarrow\uparrow\rangle$, through an angle $\phi = J(\varepsilon)\tau_E/\hbar$. The case $J(\varepsilon)\tau_E/\hbar = \pi$ constitutes a SWAP operation, rotating the state $|\uparrow\downarrow\rangle$ into the state $|\downarrow\uparrow\rangle$.

Figure 4B shows $P_S(\varepsilon,\tau_E)$ oscillating as a function of both τ_E and ε, with minima of the singlet probability corresponding to $J(\varepsilon)\tau_E/\hbar = \pi, 3\pi, 5\pi,\ldots$. The inset shows theoretical predictions $P_S = \{1 + \cos[J(\varepsilon)\tau_E/\hbar]\}/2$, using values for $J(\varepsilon)$ obtained independently from the S-T_+ resonance measurement as in Fig. 2C. In Fig. 4C, we plot exchange oscillations at the four values of detuning marked by the dashed lines in Fig. 4B. Data are fit using an exponentially damped cosine with offset, amplitude, decay time, and phase as fit parameters. To achieve faster π-pulse times, $J(\varepsilon)$ can be increased by setting V_T to increase interdot tunnel coupling and by moving to less negative (or even positive) detunings during the exchange pulse (Fig. 4D). The fastest π-pulse time obtained using these methods is ~350 ps (*33*).

We note that the observed decay time of Rabi oscillations is proportional to the Rabi period, suggesting that dephasing scales with the value of $J(\varepsilon)$ during the exchange pulse and may reflect gate noise during the τ_E interval. The contrast (~45%) seen in Fig. 4, B and C, is consistent with the contrast obtained in the singlet separation measurement of T_2^*.

Singlet-triplet spin-echo. Voltage-controlled exchange provides a means of refocusing the separated singlet to undo dephasing due to the local hyperfine fields. The pulse sequence is shown in Fig. 5A and is similar to refocusing sequences used in nuclear magnetic resonance (*34*, *35*). The separated singlet S will dephase at large negative detuning [$J(\varepsilon) \sim 0$] due to local hyperfine fields after a separation time τ_S. In the Bloch sphere representation, hyperfine dephasing results in a rotation by a random nuclear-field–dependent angle about the x axis. Thus, in each run the Bloch vector rotates by a random amount about the x axis. The dephased (1,1) state can be refocused to S by applying a pulse of finite exchange $J(\varepsilon)$ for a time τ_E, where $J(\varepsilon)\tau_E/\hbar = \pi, 3\pi, 5\pi,\ldots$, which rotates the Bloch vector around the z axis by an angle $\pi, 3\pi, 5\pi,\ldots$, and waiting for a time $\tau_S' = \tau_S$.

The singlet probability $P_S(\varepsilon,\tau_E)$ measured using the spin-echo sequence (Fig. 5A) is shown as a function of detuning and τ_E in Fig. 5B. Singlet recoveries (black regions) are observed for π, 3π, and 5π exchange pulses. A plot of the theoretical prediction $P_S = \{3 - \cos[J(\varepsilon)\tau_E/\hbar]\}/4$ (Fig. 5B, inset) using values

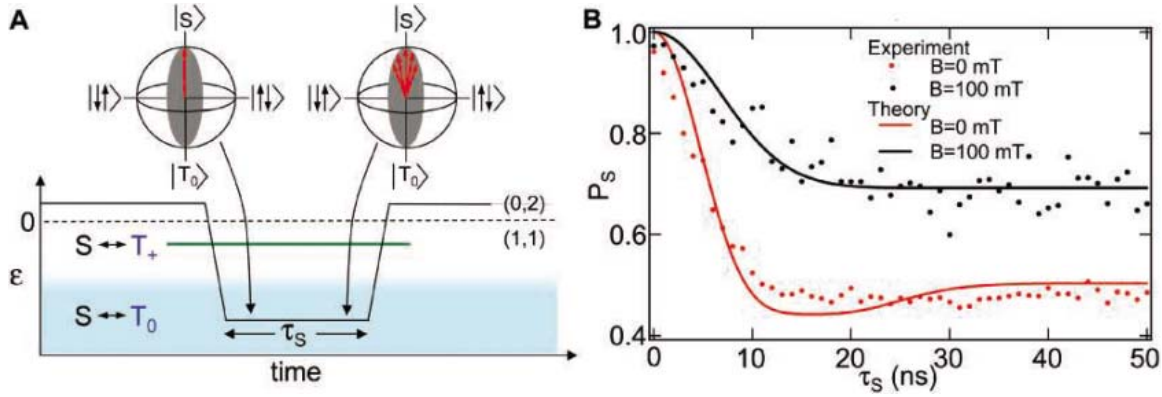

Fig. 3. (**A**) Pulse sequence used to measure T_2^*. The system is initialized into (0,2)S and transferred by rapid adiabatic passage to the spatially separated S state. With $T_\pm$ separated by a Zeeman field, S and T_0 mix at large detuning (light blue region), where hyperfine fields drive rotations about the x axis in the Bloch sphere. After a separation time τ_S, the state is projected onto (0,2)S. (**B**) Singlet probability P_S measured using the calibrated QPC charge sensor, as a function of τ_S at 100 mT (black curve) and 0 mT (red curve). For $\tau_S \ll T_2^*$, the singlet state does not have ample time to dephase, and $P_S \sim 1$. For $\tau_S \gg T_2^*$, $P_S \sim 0.7$ at 100 mT and $P_S \sim 0.5$ at 0 mT. A semiclassical model of dephasing due to hyperfine coupling (*23*) predicts $P_S \sim 1/2$ at high field and $P_S \sim 1/3$ at zero field. Fits to the model (solid curves), including a parameter adjusting measurement contrast, give $T_2^* = 10$ ns and $B_{nuc} = 2.3$ mT.

for $J(\varepsilon)$ measured independently from the S-T_+ resonance condition compares well with experiment. We note greater noise in these data than in Fig. 4. We speculate that this noise, which is ~100 times noisier than the QPC sensor readout instrument noise, is likely due to slow fluctuations in the nuclear system. Noise from a possibly similar origin was recently observed in dc transport through a double quantum dot system (*36*). Figure 5C shows P_S (red) as a function of the difference in dephasing and rephasing times, $\tau_S - \tau_S'$, for increasing values of the total time spent at large detuning, $\tau_S + \tau_S'$, averaged over 10 data sets. Differences in τ_S and τ_S' result in imperfect refocusing and decrease the recovery amplitude on a characteristic time scale $\tau_S - \tau_S' = T_2^*$.

For each value of $\tau_S + \tau_S'$, the data are fit to a Gaussian form giving $T_2^* = 9 \pm 2$ ns, consistent with measurements of the singlet decay discussed above. The best-fit heights for each $\tau_S + \tau_S'$ time are plotted as the black data points in Fig. 5C. A fit to an exponential decay with an adjustable offset to correct for the finite measurement contrast gives a characteristic coherence time of 1.2 μs, which sets a lower bound on T_2. Comparing measured values of T_2^* and this bound on T_2, we note that a simple spin-echo sequence extends the coherence time of a spatially separated singlet by more than a factor of 100. We find that two spin-echo pulse sequences applied in series (Carr-Purcell) extends the bound on T_2 by at least another factor of 2. The coherence time of our qubit using the simple spin-echo sequence exceeds the $\sqrt{\text{SWAP}}$ operation time by a factor of ~7000. Because the echo sequence relies on gate-voltage control of $J(\varepsilon)$, it is susceptible to charge dephasing during the exchange pulse. The interplay between charge dephasing during the exchange pulse and dephasing due to nuclear processes warrants further investigation (*30*, *37*).

Summary and outlook. We have demonstrated coherent quantum control of a logical qubit based on two-electron spin states. Spin states are prepared, manipulated, and measured using fast control of the exchange interaction. Rapid electrical control of the exchange interaction is used to measure T_2^*, to demonstrate Rabi oscillations and a 180-ps $\sqrt{\text{SWAP}}$ operation, and to greatly reduce dephasing of a spatially separated spin-singlet state with spin-echo techniques. Moreover, the echo sequence implements a dynamical decoherence-free subspace (*38*, *6*), which allows arbitrary two-electron spin states in S-T_0 subspace to be protected from noise. Furthermore, our results show that even in the presence of dephasing, such an encoded logical qubit can be manipulated efficiently with effectively long coherence times. This two-electron spin qubit may provide a starting point for implementation of quantum computation schemes with considerable practical advantages: All operations for preparing, protecting, and measuring entangled electron spins can be implemented by local electrostatic gate control. We anticipate that the techniques developed in this work will lead to intriguing prospects for experimental realizations of ideas from quantum information science in semiconductor nanostructures.

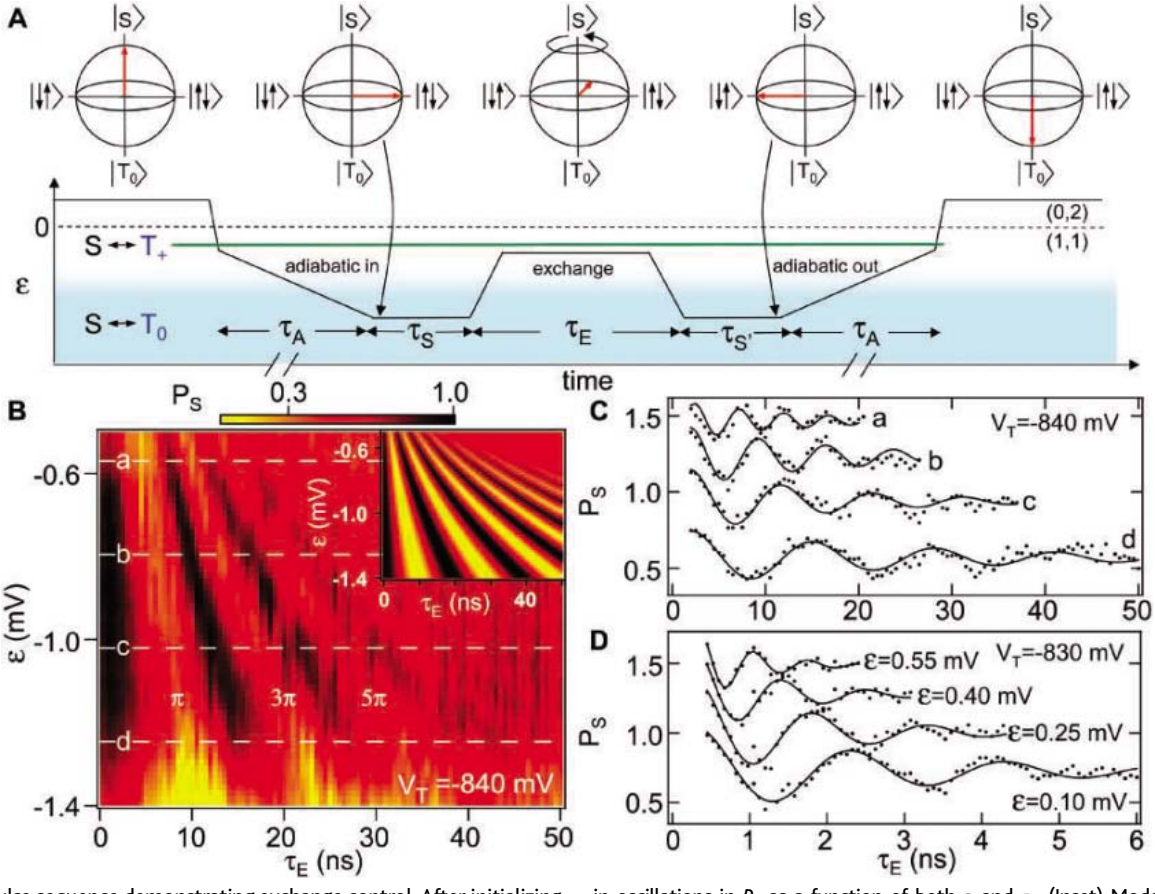

Fig. 4. (**A**) Pulse sequence demonstrating exchange control. After initializing into (0,2)S, detuning ε is swept adiabatically with respect to tunnel coupling through the S-T_+ resonance (quickly relative to S-T_+ mixing), followed by a slow ramp ($\tau_A \sim 1$ μs) to large detuning, loading the system in the ground state of the nuclear fields $|\uparrow\downarrow\rangle$. An exchange pulse of duration τ_E rotates the system about the *z* axis in the Bloch sphere from $|\uparrow\downarrow\rangle$ to $|\downarrow\uparrow\rangle$. Reversing the slow adiabatic passage allows the projection onto (0,2)S to distinguish states $|\uparrow\downarrow\rangle$ and $|\downarrow\uparrow\rangle$ after time τ_E. Typically, $\tau_S = \tau_S' = 50$ ns. (**B**) P_S as a function of detuning and τ_E. The *z*-axis rotation angle $\phi = J(\varepsilon)\tau_E/\hbar$ results in oscillations in P_S as a function of both ε and τ_E. (Inset) Model of P_S using $J(\varepsilon)$ extracted from S-T_+ resonance condition, assuming $g^* = -0.44$ and ideal measurement contrast (from 0 to 1). (**C**) Rabi oscillations measured in P_S at four values of detuning indicated by the dashed lines in (B). Fits to an exponentially damped cosine function, with amplitude, phase, and decay time as free parameters (solid curves), are shown. Curves are offset by 0.3 for clarity. (**D**) Faster Rabi oscillations are obtained by increasing tunnel coupling and by increasing detuning to positive values, resulting in a π-pulse time of ~350 ps.

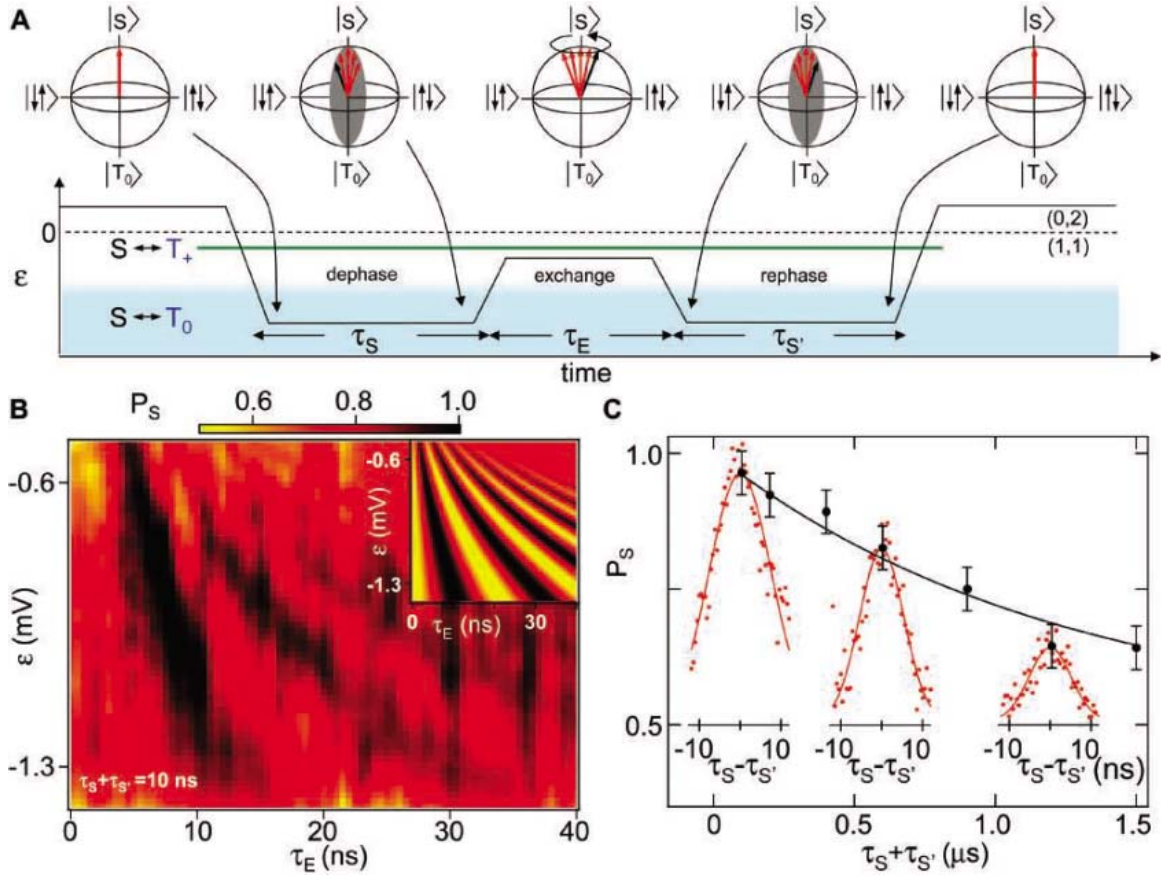

Fig. 5. (**A**) Spin-echo pulse sequence. The system is initialized in (0,2)S and transferred to S by rapid adiabatic passage. After a time τ_S at large negative detuning, S has dephased into a mixture of S and T_0 due to hyperfine interactions. A *z*-axis π pulse is performed by making detuning less negative, moving to a region with sizable $J(\varepsilon)$ for a time τ_E. Pulsing back to negative detunings for a time $\tau_S' = \tau_S$ refocuses the spin singlet. (**B**) P_S as a function of detuning and τ_E. The *z*-axis rotation angle $\phi = J(\varepsilon)\tau_E/\hbar$ results in oscillations in P_S as a function of both ε and τ_E. (Inset) Model of P_S using $J(\varepsilon)$ extracted from the S-T_+ resonance condition, assuming $g^* = -0.44$ and ideal measurement contrast (from 0.5 to 1). (**C**) Echo recovery amplitude P_S plotted as a function of $\tau_S - \tau_S'$ for increasing $\tau_S + \tau_S'$ (red points), along with fits to a Gaussian with adjustable height and width. The best-fit width gives $T_2^* = 9$ ns, which is consistent with the value $T_2^* = 10$ ns obtained from singlet decay measurements (Fig. 3B). Best-fit heights (black points) along with the exponential fit to the peak height decay (black curve) give a lower bound on the coherence time T_2 of 1.2 μs.

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31. The semiclassical model developed in (*23*, *30*) yields $P_S(\tau_S) = 1 - \frac{C_1}{2}\left(1 - e^{-(\tau_S/T_2^*)^2}\right)$ for $B \gg B_{nuc}$ and $P_S(\tau_S) = 1 - \frac{3}{4}C_2\left\{1 - \frac{1}{9}\left(1 - 2e^{-\frac{1}{2}(\tau_S/T_2^*)^2}\left\{(\tau_S/T_2^*)^2 - 1\right\}\right)^2\right\}$ for $B \ll B_{nuc}$. A fit to the 100-mT data gives $C_1 = 0.62 \pm 0.01$ and $T_2^* = 10 \pm 1$ ns. A fit to the $B = 0$ data with $T_2^* = 10$ ns fixed gives $C_2 = 0.74 \pm 0.01$.
32. We have verified that the system is in the ground state of the nuclear fields by varying the pulse parameters τ_S and τ_S'. No dependence on these parameters was observed when varied as in the singlet-triplet spin-echo measurements.
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Hsp90 Potentiates the Rapid Evolution of New Traits: Drug Resistance in Diverse Fungi

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Hsp90 is a molecular chaperone for many signal transducers and may influence evolution by releasing previously silent genetic variation in response to environmental change. In fungi separated by ~800 million years of evolution, Hsp90 potentiated the evolution of drug resistance in a different way, by enabling new mutations to have immediate phenotypic consequences. Resistance was abrogated by Hsp90 inhibitors and by febrile temperatures, suggesting new therapeutic strategies and a clinical benefit of fever. During selection in a human host, drug resistance that was initially Hsp90-dependent evolved toward independence. Thus, Hsp90 can act in diverse ways to couple environmental contingency to the emergence and fixation of new traits.

Hsp90 is an essential molecular chaperone that regulates the folding, transport, maturation, and degradation of a diverse but select set of client proteins, many of which are key regulators of cell signaling (*1*–*3*). A common feature of many Hsp90 clients is a tendency to dwell in incompletely folded or aggregation-prone states. These proteins dynamically cycle through complexes with Hsp90 and other cofactors until their activation is engendered by the proper signal.

As a consequence of its function in chaperoning regulators of cell circuitry, Hsp90 has a capacity to buffer the expression of genetic and epigenetic variation and to release it in response to environmental stress (*4*–*6*). Hsp90 is normally expressed at much higher levels than required for basal function. It is thereby intrinsically positioned to buffer variation. Protein folding, however, is exquisitely sensitive to environmental stress. Although Hsp90 is induced to cope with stress-induced problems in protein folding, depending on the genetic variants that have accumulated in particular genomes, the demand for Hsp90 can outpace its induction. In the fly *Drosophila melanogaster*, the plant *Arabidopsis thaliana*, and likely in other organisms, compromising Hsp90's buffering capacity (by drugs, mutations, or environmental stress) produces a multitude of new phenotypes. Some of these may be stochastic, but others depend on previously silent variation acting in a combinatorial manner to produce new traits (*4*, *5*). After several generations of genetic reassortment and selection, polymorphisms that had been cryptic in progenitor organisms can become so enriched in their progeny that they produce stable phenotypes even in the absence of stress (*4*). Thus, Hsp90 may play a role in evolution by acting as a capacitor for the storage and release of genetic variation.

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In cancer cells, Hsp90 may promote the evolution of new traits in a different manner. Rather than buffering the effects of new mutations, it allows them to have immediate phenotypic consequences. For example, compared to its normal cellular counterpart c-Src, oncogenic v-Src contains several mutations that both destabilize it and derepress its kinase activity (*7*). Hsp90 chaperones the unstable protein, unleashing its promiscuous kinase activities and promoting oncogenesis (*8*, *9*).

Here, we asked whether Hsp90 could allow new mutations to have immediate phenotypic consequences and promote the emergence of new traits in free-living organisms. We examined the evolution of fungal resistance to antimicrobial agents, an ancient and ubiquitous process in nature as microorganisms evolve new strategies for competition and survival. Resistant mutations are rapidly acquired (*10*); their phenotypic consequences are large (*11*); and multiple mechanisms of resistance are known (*12*, *13*). Fungal drug resistance is also of great economic and biomedical importance; few clinically useful drugs exist and resistance has emerged for all.

We investigated resistance to two classes of drugs. Azoles are the most broadly used antifungals in the clinic. They target Erg11, which is required for the biosynthesis of ergosterol, the predominant sterol of fungal membranes (*12*, *14*). Resistance arises through multiple mechanisms, including increases in Erg11 function, increases in multidrug transporters, alterations in sterol biosynthesis, and changes in membrane composition (*10*, *12*). Echinocandins, the first new antifungal class in decades, inhibit synthesis of β-(1,3) glucan, an essential component of fungal cell walls (*14*). Our results establish an entirely new facet to the role of Hsp90 in evolutionary processes.

Hsp90 potentiates the acquisition of fluconazole resistance in *S. cerevisiae*. Using the Cre-Lox system, we constructed strains of *S. cerevisiae* in which the abundance of Hsp90 could be altered by inducible recombination (*15*). These strains had a high constitutive level of Hsp90 expression that was reducible when Cre-mediated recombination removed a cassette with an Hsp90 gene (*HSC82*) and a *URA3* marker (Re90 strains, fig. S1, A to C). Other strains had either a fixed low level of Hsp90 (Lo90 strains) or a fixed high level of Hsp90 (Hi90 strains); here, Cre-mediated recombination removed only a *URA3* marker (fig. S1, A to C).

All strains exhibited the same sensitivity to the most commonly used azole, fluconazole, with growth completely arrested at 16 μg/ml (fig. S1D). To select resistant mutants, we used a rapid selection regime in which large numbers of cells are plated onto medium containing a high concentration of fluconazole (128 μg/ml). Most cells underwent ~8 doublings before growth was arrested, producing many tiny, abortive colonies (Fig. 1A). Intermediate-sized colonies were also recovered, but upon retesting, these did not have true resistance [see (*15*)]. Only colonies of the largest size (≥1.6 mm^2) had acquired robust, reproducible resistance.

Hsp90 had a profound impact on the number of large colonies recovered (Fischer's exact test, $P < 5 \times 10^{-85}$). From Hi90 and Re90 strains, 115 large colonies were obtained. All 24 that were retested grew vigorously with fluconazole (256 μg/ml) (Fig. 1B) (*16*). From Lo90 strains, only three large colonies were obtained. None showed true resistance upon retesting (*15*). Thus, the emergence of fluconazole resistance with this rapid selection regime depended on high levels of Hsp90.

Hsp90 plays a crucial role in these resistant phenotypes. Is Hsp90 required only to cope with the stress of the initial selection conditions, or is it intimately involved in enabling resistance? Cre recombinase was induced in 12 of the fluconazole-resistant mutants obtained by rapid selection (FLR strains, Fig. 1, B and C). In Hi90-FLR cells, Cre-mediated recombination had no effect on drug resistance in rich medium (Fig. 1C). In Re90-FLR strains, Cre-mediated recombination reduced Hsp90 expression and abolished resistance (Fig. 1C). All FLR strains were also resistant to voriconazole, a new azole with broader activity; this resistance was also abrogated when Hsp90 expression was reduced (*16*).

The role of Hsp90 depends on the mode of selection. *S. cerevisiae* cells exposed to two different selection regimes acquire fluconazole resistance by different mechanisms (*11*). To determine whether Hsp90 plays a role in both, we used six strains isolated in another laboratory, three by rapid selection (R1, R2, and R3) and three by gradual selection (G1, G2, and G3) (*11*). We compromised Hsp90 function pharmacologically with geldanamycin (GdA) or radicicol (RAD), structurally unrelated Hsp90 inhibitors that bind with high affinity to Hsp90's unusual adenosine triphosphate binding pocket (*17*, *18*). We used concentrations of GdA and

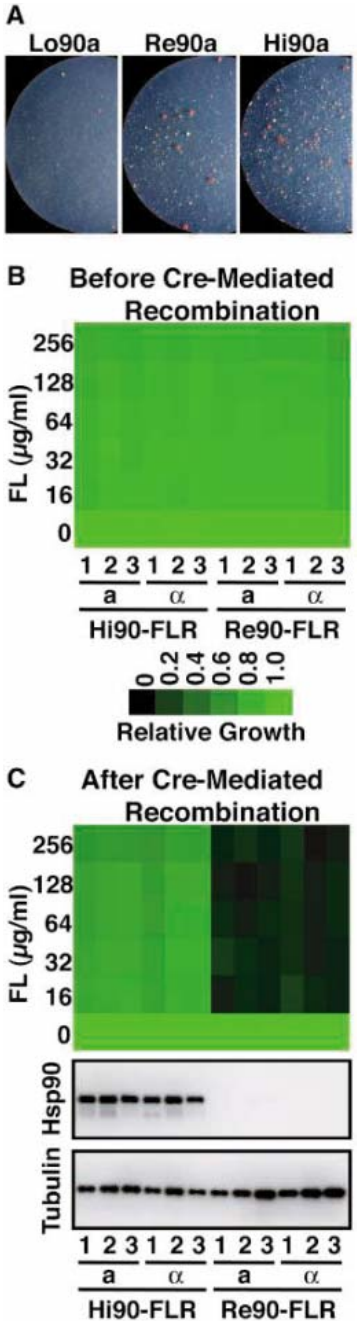

Fig. 1. Hsp90 enables rapid acquisition of fluconazole (FL) resistance and is required for its maintenance. (**A**) For both mating types (*a* and α), FL-resistant (FLR) colonies were recovered only in strains with high levels of Hsp90 (*a* shown here). Red color develops in larger colonies in this strain. (**B**) FLR strains showed strong resistance in rich medium at 23°C. Three independent Hi90-FLR and Re90-FLR strains of each mating type are shown. (**C**) Reducing Hsp90 expression by Cre-mediated recombination abrogated FL resistance. Optical densities (OD) of minimum inhibitory concentration (MIC) test plates were averaged for duplicate measurements and normalized relative to FL-free controls (see color bar). Bottom, immune blot analysis of Hsp90 levels relative to a tubulin loading control.

RAD that (i) did not impair growth on their own (Fig. 2, A to C, data points for fluconazole at 0 μg/ml); (ii) had no effect on the fluconazole sensitivities of the progenitor strains (Fig. 2A); and (iii) phenocopied the effects of genetically reducing Hsp90 in the FLR strains discussed above (*16*). GdA and RAD each abolished fluconazole resistance in the R strains (Fig. 2B), but not in the G strains (Fig. 2C). Thus, Hsp90 is required to maintain resistance acquired by rapid selection but not resistance acquired by gradual selection.

In nature, Hsp90's function can be overwhelmed by problems in protein folding that result from environmental stress, such as high temperatures (*19*). The R strains showed an enormous reduction in resistance at 39°C, whereas the G strains maintained resistance (Fig. 2D). Thus, with phenotypic consequences that are contingent on the mode of selection, environmental stress alone recapitulates the effects of impaired Hsp90 function.

Mechanism of Hsp90-independent resistance. The G strains had acquired resistance through mutations in the transcription factor Pdr1, which increase the expression of multidrug transporters such as Pdr5 (*11*). A trivial explanation for the robustness of their fluconazole resistance to GdA and RAD is that the Hsp90 inhibitors are simply being pumped out of the cell. However, G1 strains also remained resistant to fluconazole when Hsp90 was reduced genetically (fig. S2).

If this mechanism of resistance truly does not depend on Hsp90, then it should arise equally in strains with high and low levels of Hsp90 selected under a regimen that favors Pdr1-based pathways. Indeed, using such selection (*20*), triplicate populations of Hi90, Re90, and Lo90 remained static for several days and then initiated vigorous growth (fig. S3). Isolates from each population showed true resistance to fluconazole and overexpressed Pdr5 (Fig. 2E) (*16*). Thus, this mechanism of resistance can both be acquired and maintained independently of Hsp90, in contrast to the crucial role of Hsp90 in resistance acquired by rapid, acute selection.

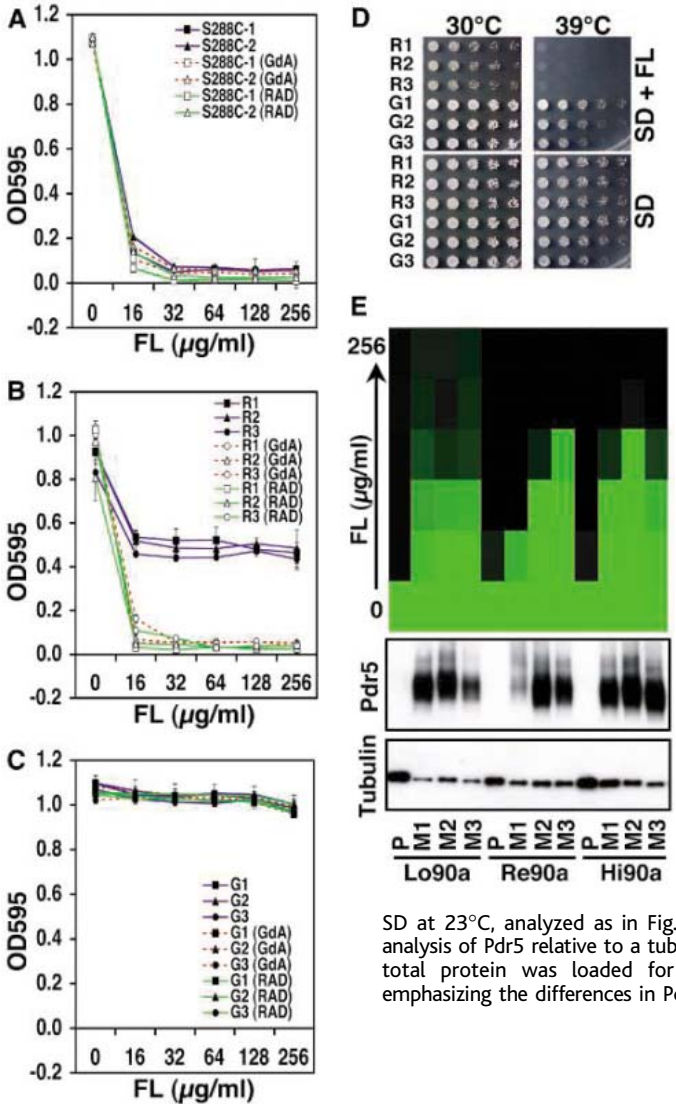

Fig. 2. Hsp90 is required for FL resistance acquired by rapid selection but not by gradual selection. Hsp90 was inhibited by geldanamycin (GdA, 5 μM) or radicicol (RAD, 5 μM) in FL MIC plates with synthetic defined (SD) medium at 30°C. (**A**) Progenitor strains; (**B**) mutants obtained by rapid selection; (**C**) mutants obtained by gradual selection. ODs of MIC test plates were averaged for three replicates. Error bars are standard deviations. (**D**) High temperature phenocopied the effects of Hsp90 inhibitors on FL resistance. Fivefold dilutions of cells (from 8×10^5/ml) were spotted on SD with FL (32 μg/ml) (top) and without FL (bottom). (**E**) Hsp90-independent FL resistance involves the increased expression of a drug pump. Top, FL resistance of the progenitor (P) and strains acquired by selection with FL (16 μg/ml) (M1 to M3) in SD at 23°C, analyzed as in Fig. 1. Bottom, immune blot analysis of Pdr5 relative to a tubulin loading control. More total protein was loaded for the progenitor strains, emphasizing the differences in Pdr5 expression.

Mechanisms of Hsp90-dependent resistance. Azoles block fungal growth by inhibiting Erg11, resulting in the accumulation of toxic intermediates in ergosterol biosynthesis (*12*). Rapid selection favors mutations in Erg3 that prevent the accumulation of toxic intermediates (*11*). Erg3 mutants have altered membrane sterol composition but can grow in the presence of azoles (*12*). Sequencing revealed that each of the 12 Hsp90-dependent strains we isolated by rapid selection contained *ERG3* mutations (table S1, Re90-FLR and Hi90-FLR).

To provide a more global view, we took advantage of a previous screen in which ~4700 viable haploid *S. cerevisiae* deletion mutants were tested for enhanced fluconazole resistance (*11*). GdA and RAD reduced resistance in all of the 11 mutants in our collection: *erg3*Δ, *erg6*Δ, *ymr102c*Δ, *ymr099c*Δ, *ypl056c*Δ, *osh1*Δ, *scs2*Δ, *cka2*Δ, *ybr147w*Δ, *ygr283c*Δ, and *ylr407w*Δ (D1 to D11, Fig. 3A) (fig. S4) (*16*). Clearly, Hsp90 can potentiate fluconazole resistance acquired through a variety of genetic lesions.

The role of calcineurin. Calcineurin is an Hsp90 client protein that regulates numerous responses to environmental stimuli, including the response to azoles (*21*–*23*). Hsp90 directly interacts with calcineurin and keeps it poised for activation (*24*, *25*). If Hsp90's effects on fluconazole resistance work through calcineurin, then inhibition of calcineurin should phenocopy Hsp90 inhibition.

Cyclosporin A (CsA) and FK506 are structurally unrelated drugs that block calcineurin function in different ways (*26*). CsA forms an inhibitory calcineurin-drug-protein complex involving Cpr1, a peptidyl-prolyl cis-trans isomerase (cyclophilin A). FK506 forms a different calcineurin-drug-protein complex involving FKBP12, a structurally unrelated peptidyl-prolyl cis-trans isomerase. Each drug strongly reduced fluconazole resistance in every one of the Hsp90-dependent mutants we tested (Fig. 3A) (fig. S4) (*16*). Thus, Hsp90 may potentiate the resistance of many different mutants through a common regulator, calcineurin.

Next, we used an *erg3*Δ mutant to dissect the underlying molecular mechanism genetically. If CsA reduced fluconazole resistance by inhibiting calcineurin, then deletion of *CPR1* should allow the *erg3*Δ mutant to maintain resistance even when CsA is present (because the inhibitory calcineurin-drug-Cpr1 complex cannot form). This was indeed the case (Fig. 3B). As expected because Hsp90 chaperones the catalytic subunit, resistance of the *erg3*Δ*cpr1*Δ double mutant was still abrogated by Hsp90 inhibitors (Fig. 3B).

Finally, we confirmed the role of calcineurin genetically. Calcineurin is a heterodimer of a catalytic subunit (either Cna1 or Cna2) and an activating regulatory subunit (Cnb1). Double mutants *erg3*Δ*cna1*Δ or *erg3*Δ*cna2*Δ were resistant to fluconazole, consistent with catalytic subunit redundancy (Fig. 3C); *erg3*Δ mutants missing both catalytic subunits (*erg3*Δ*cna1*Δ*cna2*Δ) or missing the activating subunit (Δ*erg3*Δ*cnb1*) were sensitive. Thus, calcineurin is a critical mediator of Hsp90-dependent azole resistance.

Hsp90 potentiates the evolution of drug resistance in *Candida albicans*. *C. albicans* is an important human pathogen estimated to have diverged from *S. cerevisiae* ~800 million years ago (*27*). In *S. cerevisiae*, rapid selection favors recessive *ERG3* mutations. Because *C. albicans* is diploid, we used both a standard lab strain (CAI4) and a heterozygous *ERG3* deletion mutant (CaERG3/erg3). Both were sensitive to fluconazole, with growth completely arrested at 16 μg/ml (*16*). When large numbers of cells were plated on fluconazole (128 μg/ml), many colonies were recovered (Fig. 4A). RAD had no effect on growth in the absence of fluconazole (fig. S5). However, when cells were plated on medium with fluconazole and RAD, no resistant colonies were recovered.

Heterozygosity for *ERG3* did not produce more resistant colonies, which suggests that recessive *ERG3* mutations were not the main route to resistance. Indeed, none of the six strains we analyzed carried *ERG3* mutations (*16*). Thus, although distinct underlying mechanisms may be involved, Hsp90 plays a central role in facilitating the rapid acquisition of resistance in both *C. albicans* and *S. cerevisiae*.

Evolution of *C. albicans* drug resistance in a human host. To investigate the impact of Hsp90 on a natural evolutionary process, we used *C. albicans* clinical isolates (CaCi) collected from a single HIV-infected patient over a 2-year course of fluconazole treatment. They represent a single strain that evolved increasing levels of resistance by multiple mechanisms (*28*).

All clinical isolates were more resistant than the lab strain (CAI4) to fluconazole. Differences among clinical isolates were less apparent in rich medium (Fig. 4B) than in a defined medium that mimics the nutrient-poor environment in humans (Fig. 4C). In both media, inhibition of Hsp90 (by GdA) or of calcineurin (by CsA) reduced resistance (Fig. 4B) (*16*). Both inhibitors affected early isolates more strongly than later isolates. With respect to the effects of environmental stress, febrile temperatures reached in humans confronted by infections phenocopied the effects of Hsp90 inhibition (Fig. 4C) (*16*). Thus, under the continued selective pressures shaping pathogen evolution in this patient, resistance traits initially completely dependent on Hsp90 and calcineurin evolved toward independence, with environmental stress likely providing a driving force.

Hsp90 modulates caspofungin resistance in *Aspergillus terreus*. Finally, we turned to *Aspergillus*, filamentous ascomycetes that diverged from *Candida* and *Saccharomyces* ~1 billion years ago (*27*). They are important human pathogens and are resistant to

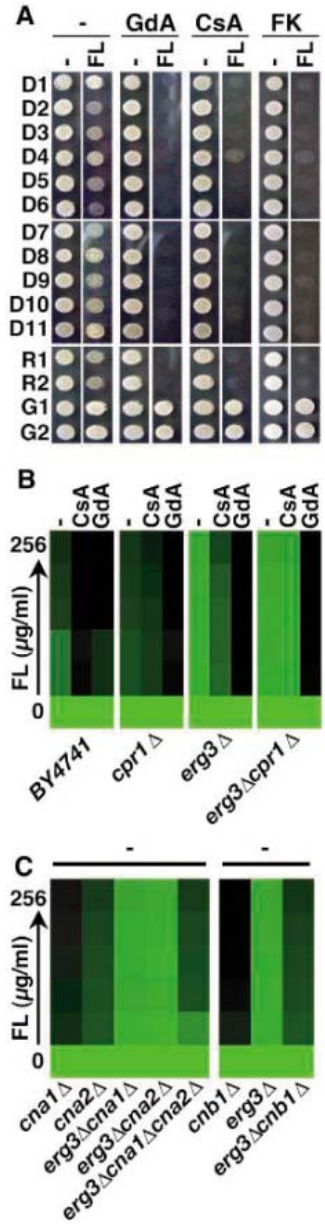

Fig. 3. Hsp90 and calcineurin are required for FL resistance acquired through diverse mutations. (**A**) Cells (4×10^6/ml) were spotted on rich medium with or without FL (64 μg/ml) at 30°C. Top two panels, deletion mutants; bottom panel, strains obtained by rapid (R1, R2) and gradual (G1, G2) selection. Hsp90 was inhibited by GdA (5 μM); calcineurin was inhibited by cyclosporin A (CsA, 20 μM) and FK506 (FK, 10 μM). Concordant results were obtained by MIC testing, but the magnitude of the inhibitors' effects on resistance differed among mutants (fig. S4). (**B**) FL resistance of the parental strain (BY4741) and *erg3*Δ and *cpr1*Δ single and double mutants in rich medium at 30°C, with CsA (20 μM), or with GdA (5 μM), analyzed as in Fig. 1. (**C**) FL resistance of *erg3*Δ and calcineurin mutants in rich medium at 30°C.

many antifungal drugs (*29*). We used antifungal test strips to create a gradient of drug concentration in solid medium. Hsp90 and calcineurin inhibitors strongly reduced the resistance of a clinical isolate of *C. albicans* to fluconazole and voriconazole, but did not affect the basal resistance of *A. terreus* (Fig. 5). Calcineurin inhibitors increase the sensitivity of *Aspergillus* to the echinocandin caspofungin (*30*, *31*). An Hsp90 inhibitor had an equally strong effect (Fig. 5). We found similar effects on clinical isolates of *A. fumigatus* (*32*). In contrast, inhibitors of calcineurin or Hsp90 did not alter the sensitivity of *C. albicans* to caspofungin (Fig. 5). Thus, Hsp90 has profound but distinct effects on drug resistance in evolutionarily distant fungal pathogens.

Discussion. Our results establish a distinct role for Hsp90 in the evolution of adaptive traits. In *S. cerevisiae* and *C. albicans*, fungal species separated by ~800 million years of evolution, Hsp90 potentiates the emergence of azole resistance by enabling diverse new mutations to have immediate phenotypic consequences. In *A. terreus*, Hsp90 is required for the high basal resistance to an echinocandin. Hsp90's role in drug resistance is to enable crucial responses to specific stresses, namely changes in the composition of cell membranes and cell walls. In this respect Hsp90 functions in concert with calcineurin, itself a key sensor of environmental stress and regulator of cell signaling.

Previous work suggests that Hsp90 might affect the evolution of new traits in two different ways. First, Hsp90 can promote the storage of cryptic genetic variation; when Hsp90 buffering capacity is compromised, new traits appear (*4*, *5*). Second, Hsp90 can chaperone mutated cell regulators that are prone to misfolding but have activated oncogenic potential (*9*, *17*); when Hsp90 function is compromised, new traits are lost. In the evolution of fungal drug resistance, new traits are also lost when Hsp90 function is compromised. Here, however, Hsp90 does not directly chaperone and activate mutated proteins. Rather, mutated proteins lose function, and it is their loss of function that confers resistance. Hsp90 chaperones a normal (unmutated) regulator of cell signaling (calcineurin), potentiating the circuitries that sculpt adaptive phenotypes. Because many mutations are expected to exert stress on cellular processes and because Hsp90 chaperones so many signal transducers, this Hsp90-mediated mechanism for the evolution of new traits is likely to play a much broader role than in the evolution of drug resistance alone. Further, although these three ways by which Hsp90 affects the acquisition of new traits were uncovered in different model organisms, they are likely to operate in the same organisms in concert.

Hsp90's role in the evolution of fungal drug resistance has broad therapeutic implications. Calcineurin inhibitors have antifungal potential, but their immunosuppressant effects are problematic (*33*). Hsp90 inhibitors might provide a better strategy. Drugs structurally related to GdA are currently in phase I/II clinical trials as anticancer agents (*34*, *35*). Hsp90 inhibitors are effective in overcoming fungal drug resistance at concentrations that are clinically well tolerated. Inhibiting Hsp90 may render resistant fungal pathogens more responsive to treatment and, when given early in therapy, may impede the de novo evolution of resistance. Hsp90 inhibitors may provide an even broader therapeutic paradigm; calcineurin and Hsp90 inhibitors also have potent antimalarial activity (*25*).

Hsp90 is a central player in the ancient and highly conserved heat-shock response. Although Hsp90 is induced in response to heat stress, its capacity to maintain client proteins can be compromised by severe stress. One form of heat shock, fever, is a conserved response to infection. The potential risks and benefits of fever to the infected host remain difficult to decipher (*36*). Increased temperatures can abolish fungal drug resistance, which provides an explicit mechanism by which fever, in the modern era, might be beneficial to the host. Historically, fever may have benefited the host by sensitizing the cellular circuitry of fungal pathogens and impeding the deployment of other virulence mechanisms.

Strikingly, traits acquired by different Hsp90-mediated effects can evolve to have little dependence on Hsp90. This can occur through the enrichment of preexisting polymorphisms during continued rounds of mating and selection (*4*). Here, in fungi, this occurred via additional mutations. Repeated episodes of fever may provide

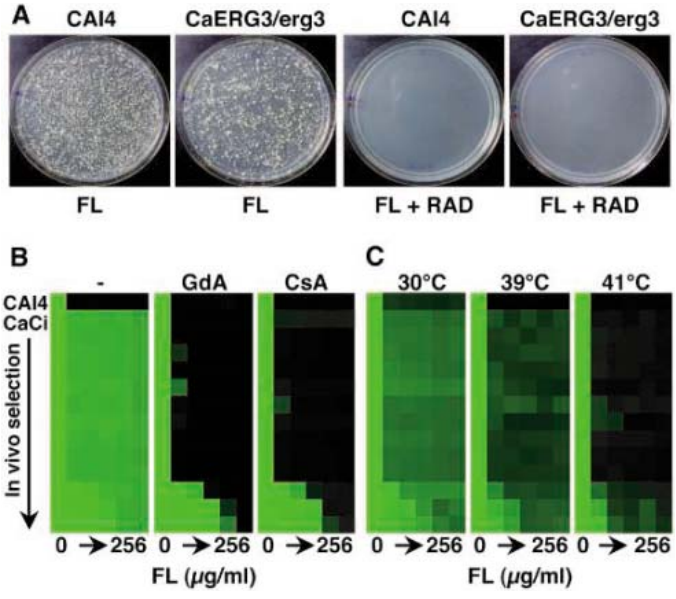

Fig. 4. The importance of Hsp90 in FL resistance in *C. albicans*. (**A**) Hsp90 inhibition blocked the emergence of FL resistance in a strain wild-type for *ERG3* (CAI4) and a heterozygous *ERG3* deletion mutant. Left, selection with FL (128 μg/ml) alone; right, selection with FL plus 1 μM RAD. (**B**) FL resistance of clinical isolates was initially Hsp90-dependent but evolved toward independence. Left, FL sensitivity of CAI4 and resistance of serial clinical specimens (CaCi) isolated from an HIV patient receiving FL; isolates are ordered sequentially, with those recovered early at the top. Middle and right, inhibition of Hsp90 by GdA (5 μM) or calcineurin by CsA (20 μM) in rich medium with FL at 30°C, analyzed as in Fig. 1. (**C**) Elevated temperatures reduce FL resistance of CaCi isolates in synthetic medium (RPMI).

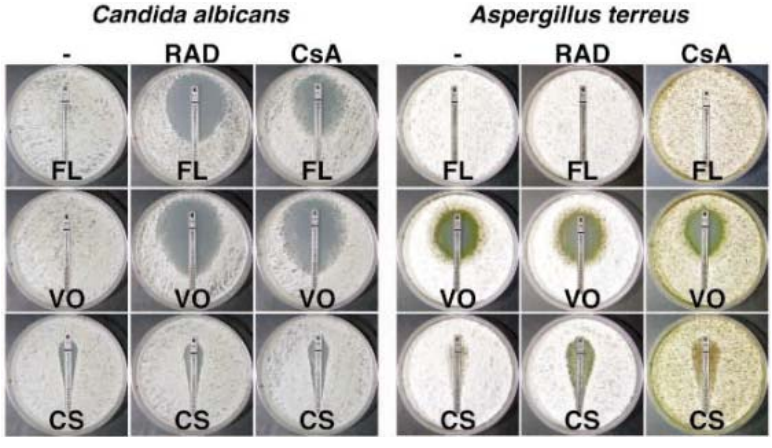

Fig. 5. Hsp90 potentiates resistance to different drugs in *C. albicans* and *A. terreus*. Resistance of *C. albicans* clinical isolate T118 and *A. terreus* soil isolate ATCC 10020 to two azoles [fluconazole (FL) and voriconazole (VO)] and to an echinocandin [caspofungin (CS)] is shown on rich medium. Antifungal test strips (Etest, AB Biodisk) produce a gradient of drug concentration, highest at the top (*15*). Plates contained RAD (5 μM) or CsA (20 μM). For MIC values, see table S2.

ideal selective conditions for the emergence of Hsp90 independence. A very different way in which changes in protein folding can potentiate the acquisition of new traits and provide a route to their genetic assimilation has been described for a yeast prion (*37*). There will likely be many other mechanisms by which spontaneous and environmentally induced changes in protein folding (*19*) and cell signaling (*38*, *39*) promote the emergence of new traits.

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Materials and Methods
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REPORTS

Influence of Gravity Waves on the Internal Rotation and Li Abundance of Solar-Type Stars

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The Sun's rotation profile and lithium content have been difficult to understand in the context of conventional models of stellar evolution. Classical hydrodynamic models predict that the solar interior must rotate highly differentially, in disagreement with observations. It has recently been shown that internal waves produced by convection in solar-type stars produce an asymmetric, shear layer oscillation, similar to Earth's quasi-biennial oscillation, that leads to efficient angular momentum redistribution from the core to the envelope. We present results of a model that successfully reproduces both the rotation profile and the surface abundance of lithium in solar-type stars of various ages.

Rotation plays a crucial role in stellar evolution. Low-mass stars, including the Sun, are known to start their life with a large surface rotational velocity and then spin down with time because of a magnetically dominated stellar wind linked to their external convection zones. The interplay between the loss of angular momentum through a wind and its redistribution inside the star creates velocity gradients that induce mixing of elements. In the case of a fragile element such as lithium, which is destroyed by proton capture at a relatively low temperature (~2.5 million degrees) not too far below the convection envelope, surface depletion is thus expected. The lithium atmospheric abundance has been determined in many stars for which a fair estimate of the mass and age is feasible. These data allow an estimate of the extent, magnitude, and temporal evolution of chemical transport in the outermost stellar radiative regions, which may be linked directly to the instantaneous distribution of angular momentum in these objects. Furthermore, the quasi-flat seismic solar rotation profile (*1*, *2*) tells us that the characteristic time scale for the evolution of angular momentum has to be shorter than the age of the Sun.

Sophisticated stellar models that take into account hydrodynamic processes induced by rotation (i.e., meridional circulation and shear mixing) fail to reproduce the major observational constraints described above (*3*, *4*), although they are successful in reproducing the abundance anomalies and evolution characteristics of more massive stars (*5*). For solar-type stars with relatively extended convective envelopes that are strongly spun down by magnetic braking in their infancy, these models predict large rotation gradients within the interior, which are not consistent with helioseismology (Fig. 1). This is due to the too-low efficiency of the invoked hydrodynamic instabilities in redistributing angular momentum.

Two mechanisms have been proposed to explain the near uniformity of the solar rotation profile. The first rests on the possible existence of a magnetic field in the radiation zone (*6*, *7*). The second invokes traveling internal gravity waves (IGWs) generated at the base of the convection envelope (*8*, *9*). For either of these solutions to be convincing, they must be tested with numerical models coupling these processes with rotational instabilities and should explain all the aspects of the problem, including the lithium evolution with time.

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In conjunction with turbulent viscosity, IGWs in the Earth's atmosphere lead to a phenomenon known as the quasi-biennial oscillation (or QBO), which is an alternating pattern of eastward and westward mean zonal winds observed in the stratosphere close to the equator. This feature has long been known by atmospheric scientists but could be explained only when waves were added to numerical models of the atmosphere (*10*, *11*). The main reason for this is that momentum transport by waves does not have the same behavior as turbulence. First, waves take angular momentum in the region where they are produced and deposit it where they are damped, and they are thus able to accelerate regions very far from where they originate. Second, they tend to increase rather than reduce local shears.

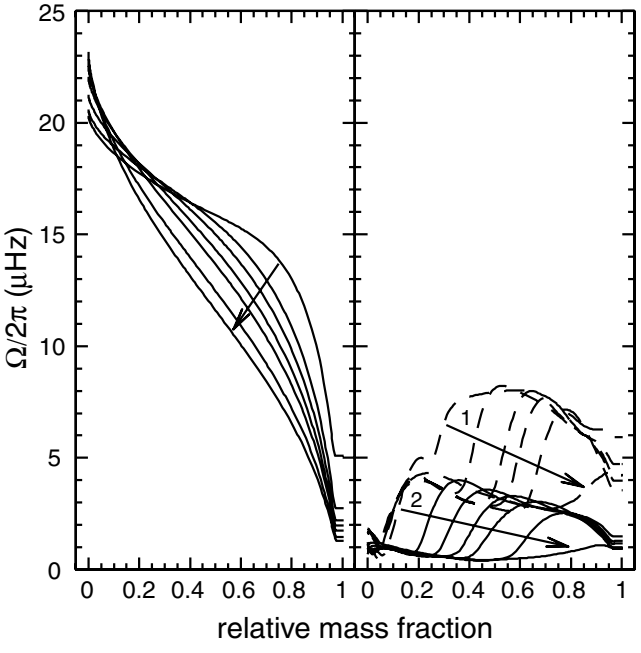

Fig. 1. Evolution of the interior rotation profile in a solar mass model with and without IGWs. The initial equatorial rotation velocity is 50 km s^{-1}, and identical surface magnetic braking is applied. (**Left**) Model without IGWs. Curves correspond to ages of 0.2, 0.5, 0.7, 1.0, 1.5, 3.0, and 4.6 billion years (Gy) and increase in the direction of the arrow. Differential rotation remains large at all times. (**Right**) When IGWs are included, low-degree waves penetrate all the way to the core and deposit their negative angular momentum in the whole radiative region. Because the core's angular momentum is minute, it is spun down very efficiently. In the so-created "slow" region, damping of retrograde waves increases, leading to the formation of a front, which propagates from the core to the surface. Curves showing propagation of the first front (labeled 1) correspond to ages of 0.2, 0.21, 0.22, 0.23, 0.25, and 0.27 Gy. Further spin-down leads to the formation of a second front (ages 0.5, 0.7, 1.0, 1.5, 3.0, and 4.6 Gy). The first front propagates faster than the second one because of stronger braking early in evolution. At the age of the Sun, the radiative region is rotating almost uniformly.

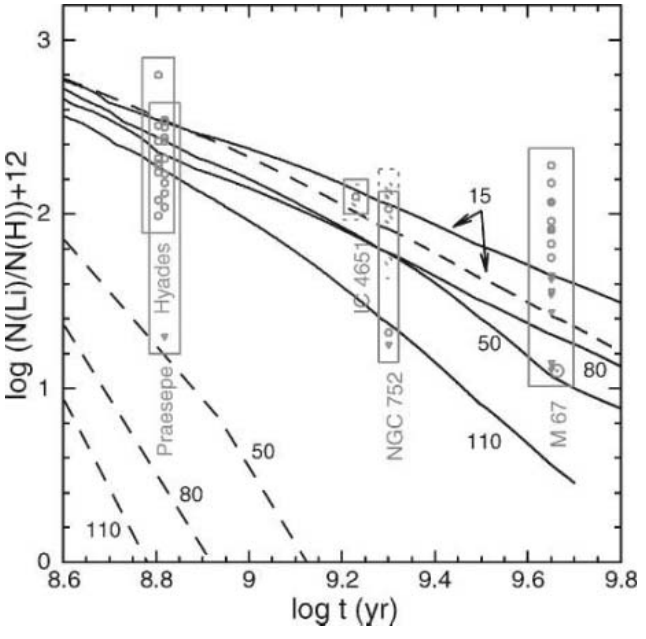

Fig. 2. Evolution of surface lithium abundance (*N* is the number abundance) with time for solar mass stars. The vertical extent of boxes shows the range of lithium values as observed in various galactic clusters (*26*–*32*) for stars with an effective temperature corresponding to that of the model ± 100 K at the cluster age, plus a typical error in abundance determination. The horizontal extent corresponds to the age uncertainty. Circles indicate abundance determinations, and triangles denote upper limits for individual stars. The solar value is shown with the usual symbol ⊙. Solid lines correspond to models including IGWs and dashed lines to models without IGWs. Initial velocities are shown on the figure (in km s^{-1}). In the cases without IGWs, except for the slowest rotator, lithium depletion is too strong, by orders of magnitude, at all ages. When included, IGWs, by changing the shape of the internal velocity gradients, lead to a decrease in the associated transport of chemicals. Lithium is then much less depleted, and predictions account very well for the data. At all considered ages, the observed dispersion in atmospheric lithium is well explained in terms of the initial velocity of each specific star. t, time in years.

In stars, IGWs are generated in the convection zone. At the convective/radiative interface, they produce a very narrow, double-peaked shear layer that oscillates on a time scale of a few years (*12*, *13*). This shear layer oscillation (hereafter SLO) is similar to the QBO. Talon, Kumar, and Zahn (*14*) explained how this feature can lead to angular momentum extraction from the deep stellar interior when the outer convective zone is rotating slower than the interior. This is due to an asymmetry of the SLO, which preferentially damps the prograde waves that carry positive angular momentum. Low-degree, low-frequency waves then deposit preferentially negative angular momentum in the interior. However, these calculations were made in a static model and did not consider the issue of mixing of light elements. Later, we developed a formalism to take into account all aspects of IGWs in the computation of complete stellar evolution models (*15*). This model relies on WKB (Wentzel, Kramers, and Brillouin) approximation for the calculation of the local wave function and assumes that damping is caused by viscous turbulence and thermal diffusivity.

We used this formalism to compute self-consistent hydrodynamic models of evolving solar mass stars, including the transport of angular momentum by meridional circulation, shear turbulence (*16*), and IGWs. Elements evolve in this model by the same physical processes plus gravitational settling and nuclear reactions. All transport properties depend on the instantaneous rotation profile and distribution of elements. Initial surface rotation velocities typical of those observed for stars in very young open clusters were used. We applied braking by magnetic torquing at the stellar surface (*17*) so as to reach the observed rotation velocity at the age of the Hyades (*18*). We considered only IGWs produced by fluctuating Reynolds stresses (*19*, *20*). The total wave energy used for these calculations was 8.5×10^{29} erg s^{-1}, that is, 0.02% of the energy of the solar convection zone. Some uncertainty remains in the wave flux we use because of the eventual contribution of convective overshooting (*21*, *22*).

Figure 1 presents the evolution of the rotation profile for two cases: when angular momentum transport is due solely to meridional circulation and shear turbulence and when angular momentum deposition by IGWs is taken into account in conjunction with these hydrodynamic processes. In the former case, differential rotation remains large throughout the evolution of the star, and its magnitude at the age of the Sun is excluded by helioseismology. When IGWs are considered, the low-degree waves penetrate all the way to the core and

spin it down extremely efficiently at the very beginning of the evolution. This is related to the small (because it is proportional to r^2) amount of angular momentum in the core. Once the core has been spun down, the damping of retrograde waves, which carry the negative angular momentum, increases locally. Consequently, a "slowliness" front forms and propagates in a wave-like way from the core to the surface. As further braking proceeds, a second front forms and propagates outward. The time scale for angular momentum extraction through differential wave filtering in a Sun-like star is of the order of a few 10^7 years (*8*, *9*). It adjusts itself so as to compensate for the flux of angular momentum that is lost through the stellar wind. This explains why front propagation is fast at the beginning and then slows down, just as the spin-down rate does.

Figure 2 shows the predicted evolution of the surface lithium abundance together with the data for solar mass stars in open clusters of various ages. In the case without IGWs, lithium depletion is always too strong. However, thanks to IGWs, the transport of elements and the resulting lithium depletion are considerably reduced because of the flattening of the internal rotation profile. Our calculations with IGWs fit the data quite well. The smallness of the observed dispersion in the lithium content is well explained even with a realistic and thus large range for the initial rotation velocity. This process is also self-regulating, and as such, our results do not depend qualitatively on the total wave flux used as long as it is large enough (that is, ~0.01% of the convective energy).

The presence of a dynamo magnetic field at the convective interface (termed a tachocline) would not qualitatively change the results presented here. A strong magnetic field (10^5 G) may prevent very low frequency waves ($\omega < 0.1$ μHz for $l = 2$, where ω is frequency and l is spherical harmonic degree) from propagating (*14*, *23*). The lowest frequency used for the calculations presented here is $\omega = 0.5$ μHz. The low-degree waves that deposit angular momentum in the interior are thus not affected. Although the disappearance of high-degree, low-frequency waves could affect SLO dynamics, this has a negligible impact on filtering (*15*), which is dominated by the velocity difference on both sides of the SLO.

These results show in principle the ability of IGWs to efficiently extract angular momentum from the deep interior of solar-type stars on a very short time scale and as such, nullify the argument made by Gough and McIntyre (*24*) about the "inevitability of a magnetic field" in the solar interior. Our hydrodynamic model, which uses the same free parameters to describe rotational mixing as those that successfully reproduce abundance anomalies in massive stars (*5*), successfully shapes both the rotation profile and the time evolution of the surface lithium abundance in these objects. In order to compare it to other models that rely on a fossil magnetic field (*25*), better helioseismic constraints are needed. The presence of a negative rotation gradient, for example, would strongly point toward wave transport. Our comprehensive picture should have implications for other difficult unsolved problems related to the transport of chemicals and angular momentum in low-mass stars. We think in particular of halo dwarf stars and the related cosmological problem of the primordial lithium and of giants on the horizontal and asymptotic giant branches that exhibit unexplained abundance anomalies.

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Imaging Spin Transport in Lateral Ferromagnet/ Semiconductor Structures

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We directly imaged electrical spin injection and accumulation in the gallium arsenide channel of lateral spin-transport devices, which have ferromagnetic source and drain tunnel-barrier contacts. The emission of spins from the source was observed, and a region of spin accumulation was imaged near the ferromagnetic drain contact. Both injected and accumulated spins have the same orientation (antiparallel to the contact magnetization), and we show that the accumulated spin polarization flows away from the drain (against the net electron current), indicating that electron spins are polarized by reflection from the ferromagnetic drain contact. The electrical conductance can be modulated by controlling the spin orientation of optically injected electrons flowing through the drain.

Three essential elements of a semiconductor spin transport device are as follows: (i) a mechanism for electrically injecting spin-polarized electrons, (ii) a practical means for spin manipulation and transport, and (iii) an electronic scheme for detecting the resulting spin po-

larization. It was recently demonstrated that ferromagnetic metals provide a source of spin-polarized electrons in devices using Schottky tunnel barriers between transition metal ferromagnets and semiconductors. Steady-state spin polarizations >25% can be maintained in structures with a ferromagnetic metal source and a light-emitting diode spin detector (*1*–*3*). The detected spins in these experiments are confined to the region immediately underneath the injector, but an independent means of manipulating the injected spins, particularly through precessional phenomena (*4*), is realized more easily in a lateral device geometry. Recent experiments have demonstrated coherent precessional phenomena over 100-μm length scales (*5*), strain-induced spin precession of lateral electron flows (*6*, *7*), current-induced spin polarization (*8*), and the spin Hall effect (*9*, *10*), providing motivation for integrating ferromagnetic spin injectors and detectors into lateral semiconductor spin-transport devices. All-metallic prototypes (*11*, *12*) with ferromagnetic contacts have been demonstrated, but experiments on analogous semiconductor devices with ferromagnetic injectors have been less conclusive (*13*–*16*), largely because there has been no demonstration of precessional phenomena in a semiconductor electrical spin-transport measurement.

Here we report the direct observation of spin injection, transport, accumulation, and detection in devices with metallic ferromagnetic source and drain contacts at opposite ends of a lightly-doped (100) *n*-type GaAs (with layers Si-doped for $n = 2 \times 10^{16}$ cm^{-3}) semiconductor channel. Each contact, which can be used as either an injector or detector, is a Schottky tunnel barrier formed by an epitaxial iron (Fe) film grown on a highly doped n^+-GaAs layer (*17*). Scanning Kerr microscopy (*7*, *9*, *18*) was used to image the spin transport in the 300-μm-long channel region. We present data from devices in which the channel is parallel to the [011] direction ($\pm\hat{x}$ direction in Fig. 1A) along the Fe magnetization vector **M**. Similar results were obtained with heterostructures from different growths and with devices having different channel and contact geometries.

The devices were mounted, strain-free, on the vacuum cold finger of an optical cryostat (temperature $T = 4$ K). Uniform uniaxial stress along the [011] GaAs axis could be applied in situ using a cryogenic vise built into the cold finger (*7*). In the *n*-GaAs channel (Fig. 1A), the $\hat{z}$ component of the conduction electron spin polarization (S_z) was measured by detecting the Kerr (light polarization) rotation angle θ_K of a linearly polarized probe laser that was reflected from the sample at normal incidence (*17*). Positive θ_K indicates positive S_z.

Images of the steady-state electron spin polarization S_z in the *n*-GaAs channel near the source and drain contacts (Fig. 1B) at a bias voltage $V_b = +0.4$ V show injection and lateral flow of spin-polarized electrons. These electrons have initial spin **S** along **M** ($\pm\hat{x}$). Without a magnetic field along $\hat{y}$, **S** remains in-plane, yielding $S_z = 0$ and no Kerr rotation θ_K. These images were therefore obtained using a small in-plane magnetic field ($B_y = +3.6$ G), which forces the injected electrons to precess in the *x*-*z* plane. With **M** parallel to $-\hat{x}$ as shown, measuring θ_K ($\propto S_z$) versus B_y (Fig. 1C) confirms that the injected electrons have initial spin **S** that is antiparallel to **M** and therefore parallel to the majority electron spin polarization in Fe. Reversing B_y inverts the direction of spin precession, so that θ_K changes sign. We note that $\theta_K(B_y)$ inverts when **M** is reversed, as expected. By comparison with optical pumping results, we estimate the injected electron spin polarization to be 5 to 10%. No spin precession signal is observed anywhere in a control device with aluminum contacts.

The decay length of the injected spin polarization (~50 μm) is much less than the 300-μm channel length. Therefore, the injected spins lose polarization long before they reach the drain contact. However, the right-hand side of Fig. 1B reveals an appreciable electron spin polarization in the channel within ~10 μm of the drain. The sign of θ_K and the shape of the $\theta_K(B_y)$ curves (Fig. 1D) are the same as for the injected electrons near the source. Therefore, the electron spin polarization that accumulates near the Fe drain contact is also oriented antiparallel to **M** (along $\pm\hat{x}$).

We determined the momentum (**k**) direction of the spin-polarized electrons near the drain by exploiting symmetries of the effective magnetic fields that arise from strain-induced spin-orbit coupling in GaAs. Spin precession of flowing electrons can be observed in strained samples (*6*), and the ef-

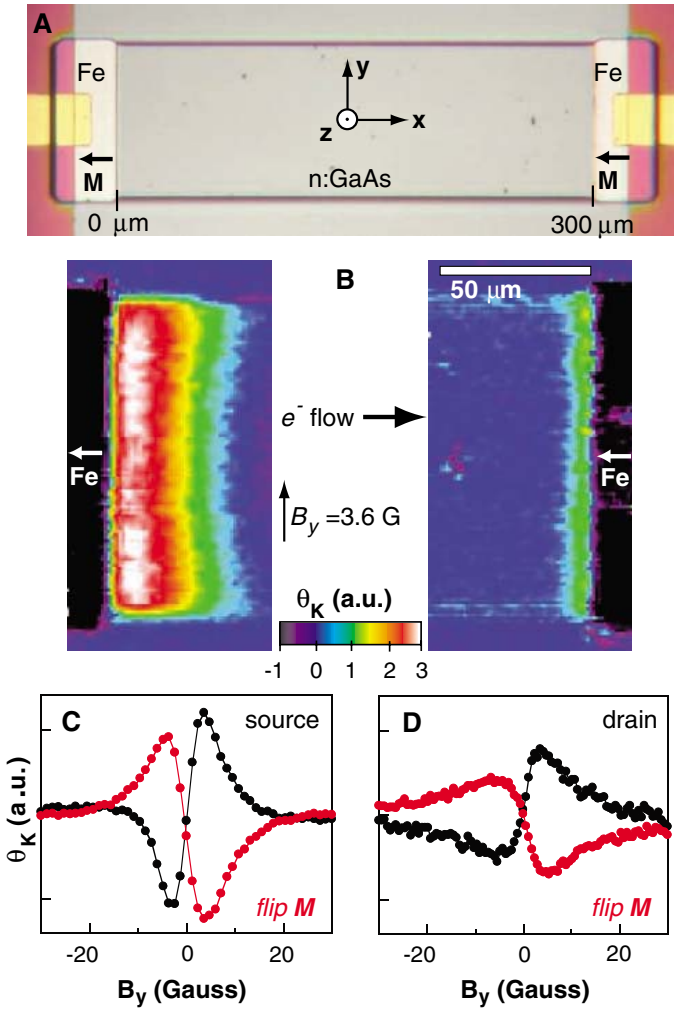

Fig. 1. (**A**) Photomicrograph of the lateral ferromagnet/semiconductor device used for electron spin injection, transport, accumulation, and detection. The Fe/GaAs Schottky tunnel barrier source/drain contacts have [011] easy-axis Fe magnetization **M** along $-\hat{x}$ as shown. The *n*-GaAs channel is 300 μm × 100 μm. (**B**) Images of Kerr rotation angle θ_K ($\propto S_z$) near the source and drain contacts. $V_b = +0.4$ V. The region of spin accumulation near the drain contact also exhibits positive θ_K, indicating that both the injected and accumulated spin polarizations are antiparallel to **M**. (**C**) θ_K versus B_y measured in the *n*-GaAs channel at a point ~10 μm from the source contact, with **M** antiparallel (black) and parallel (red) to $\hat{x}$. $V_b = +0.4$ V. (**D**) Same as (C), but measured at a point 4 μm from the drain contact ($x = 296$ μm). a.u., arbitrary units.

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fective fields themselves can be controlled with uniaxial stress along the <011> axes (*7*). The uniaxial stress couples electron spin σ to the off-diagonal elements $\varepsilon_{\alpha\beta}$ of the crystallographic strain tensor. For electrons moving laterally in the *x*-*y* sample plane, the spin-orbit Hamiltonian is $H_S \propto \varepsilon_{\alpha\beta}(\sigma_y k_x - \sigma_x k_y)$ (*19*), which describes an effective magnetic field $\mathbf{B}_\varepsilon$ that is in-plane and orthogonal to **k**. Electrons with **k** parallel to $+\hat{x}$ (Fig. 1A) precess about an effective magnetic field that is parallel to $+\hat{y}$, whereas electrons with momentum –**k** precess in the opposite direction about an effective magnetic field that is parallel to $-\hat{y}$. Thus, $\mathbf{B}_\varepsilon$ either augments or opposes the applied field B_y, shifting the $\theta_K(B_y)$ curves to the right or left depending on the spin flow direction. Small [011] stresses were applied to the device substrate, and $\varepsilon_{\alpha\beta}$ was measured by the GaAs band-edge blue shift (*7*). The resulting effective field $\mathbf{B}_\varepsilon$ (parallel to $\pm\hat{y}$) induces spin precession in the *x*-*z* plane, even when $B_y = 0$ (Fig. 2A). These images also reveal the polarization that accumulates near the drain contact; however, the sign of θ_K is negative—opposite to that of the injected electrons—and in direct contrast with Fig. 1B, which was acquired with a real magnetic field B_y. The $\theta_K(B_y)$ curves measured near the source contact (Fig. 2B) shift to the left with increasing stress ($\mathbf{B}_\varepsilon$ parallel to $+\hat{y}$), whereas curves measured near the drain (Fig. 2C) shift to the right ($\mathbf{B}_\varepsilon$ parallel to $-\hat{y}$). Therefore, the spin-polarized electrons near the source and drain contacts move in opposite directions, indicating that the polarized spins near the drain are traveling along $-\hat{x}$, against the net electron current and away from the drain. These results demonstrate explicitly that electrons near the drain contact become polarized by spin-dependent reflection from the Fe/GaAs tunnel barrier.

Spin polarization by reflection from a ferromagnet/semiconductor interface has been studied theoretically (*20*) and was observed by using optical pumping (*21*, *22*) and in GaAs/MnAs Schottky diodes (*18*) under large forward bias (>1 V). Given the low-resistance tunnel junctions in the present design, spin accumulation is observed at biases down to 50 mV, for which the small drift velocity allows electrons polarized by reflection to diffuse "backstream" into the channel by nearly one spin diffusion length (~10 μm). In all devices and for all device biases $0.050\ \text{V} \le V_b \le 1.0\ \text{V}$, the accumulated (and injected) spin polarization is antiparallel to **M**.

Figure 3A shows $\theta_K(B_y)$ curves acquired in the *n*-GaAs channel, 65 μm from the source contact. In contrast to measurements near the contacts, these data exhibit multiple oscillations. We consider a simple model for spin transport in the channel. Spin-polarized electrons, injected with $S_0 = S_x$ (at $x = 0$ and time $t = 0$) and having a drift velocity v_d, precess as they flow down the channel, arriving at the point of detection x_0 at a later time $t = x_0/v_d$. At this point, $S_z = S_0 \exp(-t/\tau_s)\sin(\Omega_L t)$, where τ_s is the spin lifetime and $\Omega_L = g_e\mu_B B_y/\hbar$ is the Larmor precession frequency, where g_e is the electron *g* factor, μ_B is the Bohr magneton, and $\hbar$ is Planck's constant divided by 2π. The actual signal is therefore computed by averaging the spin orientations of the precessing electrons over the Gaussian distribution of their arrival times (which has a half-width determined by diffusion)

$$S_z(B_y) = \int_{x_0}^{x_0+w}\int_0^\infty \frac{S_0}{\sqrt{4\pi Dt}} e^{-(x - v_d t)^2/4Dt} \times e^{-t/\tau_s}\sin(\Omega_L t)\,dt\,dx \quad (1)$$

where *D* is the diffusion constant, $v_d = \mu E$ is the drift velocity, μ is the electron mobility and *E* is the electric field, and the spatial integral accounts for the width *w* of the source contact (*23*). This type of averaging is the basis of the Hanle effect observed in optical pumping experiments and previous spin-transport experiments in metals (*11*, *12*) and semiconductors (*4*, *8*, *18*, *24*). A calculation of S_z at $x_0 = 65$ μm is shown in Fig. 3A. Good agreement with the data are obtained using $D = 10\ \text{cm}^2/\text{s}$, $v_d = 2.8 \times 10^4$ cm/s, and $\tau_s = 125$ ns. The large drift velocity and spin lifetime in our devices allow access to a spatial regime far from the contacts and well beyond a spin diffusion length ($x_0 > \sqrt{D\tau_s}$), in which the average time of flight from the source to the point of detection, $T = (x_0 + w/2)/v_d$, determines the "age" of the measured spins. In this limit, the first peak in the data ($B_y = B_{peak}$) is the field in which electrons precess through one-quarter Larmor cycle, so that $T = \pi/(2\Omega_L) = \pi\hbar/(2g_e\mu_B B_{peak})$. In Fig. 3A, $x_0 = 65$ μm and $B_{peak} = 1.35$ G, indicating that $T \sim 300$ ns, and $v_d \sim 2.8 \times 10^4$ cm/s.

At a fixed bias, Fig. 3B shows $\theta_K(B_y)$ curves acquired at 16-μm increments from the source contact, demonstrating that injected spins are readily observable up to 120 μm from the source. Further from the source, the average age of the measured spins increases. As a result, B_{peak} decreases, and the amplitude of the signal decreases because of spin relaxation. Figure 3C shows similar data acquired at 2-μm intervals from the drain contact, demonstrating the much shorter length scale for spin accumulation. The evolution of the $\theta_K(B_y)$ curves near both contacts is captured very well by Eq. 1 with a single set of parameters (fig. S2, A and B). Strain effects are modeled using the approach of (*7*), and the results (fig. S2, C and D) show good qualitative agreement with the data of Fig. 2, B and C.

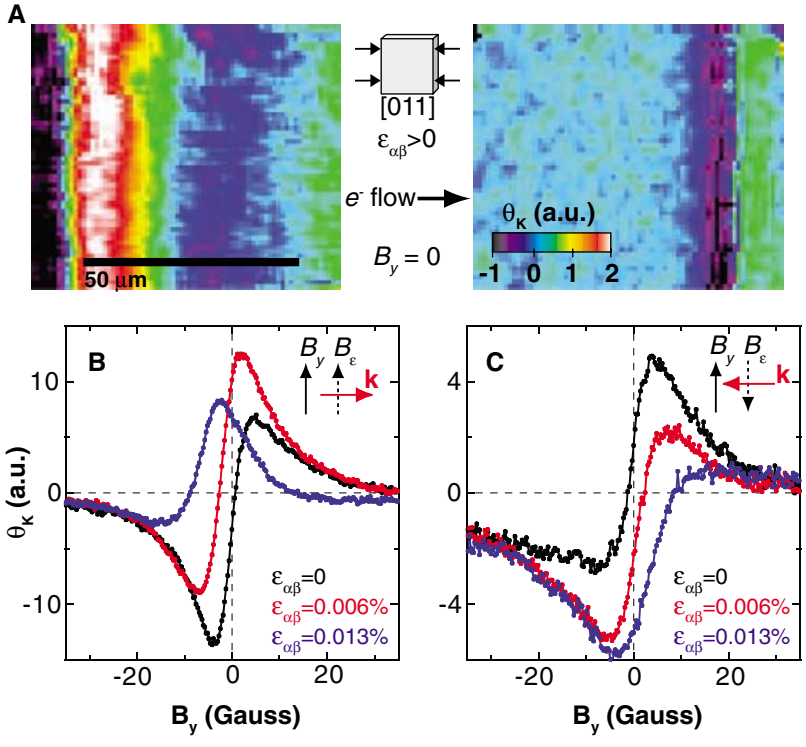
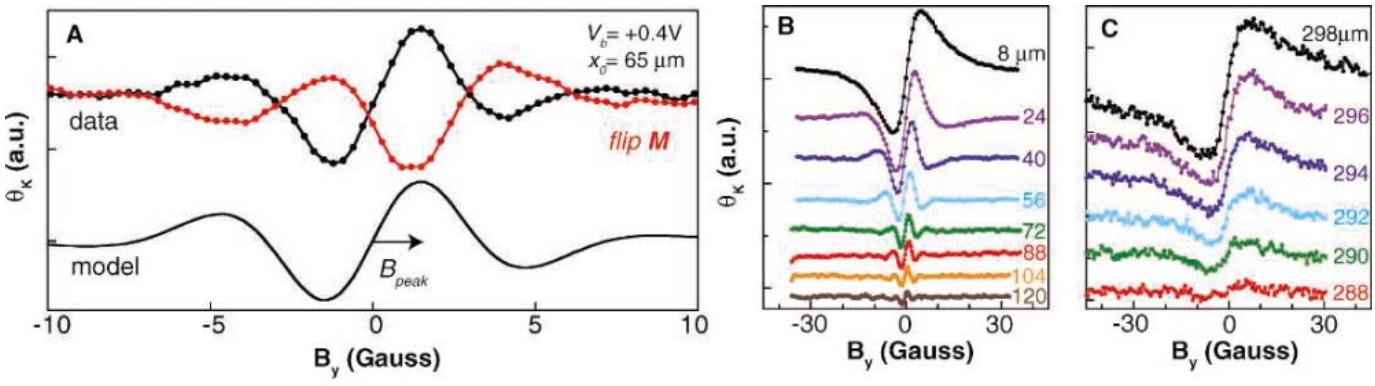


Fig. 2. (**A**) Images of θ_K near the source and drain contacts, in the presence of a small effective magnetic field $\mathbf{B}_\varepsilon$ induced by off-diagonal strain $\varepsilon_{\alpha\beta}$ (due to applied [011] uniaxial stress). $B_y = 0$ and $V_b = +0.4$ V. (**B** and **C**) $\theta_K(B_y)$ curves acquired at points 4 μm from (B) the source and (C) the drain contact, for three values of uniaxial stress. Curves shift to the left at the source contact and shift to the right at the drain contact, indicating that the spin-polarized electrons accumulated near the drain contact are flowing away from the drain (against the net electron current).



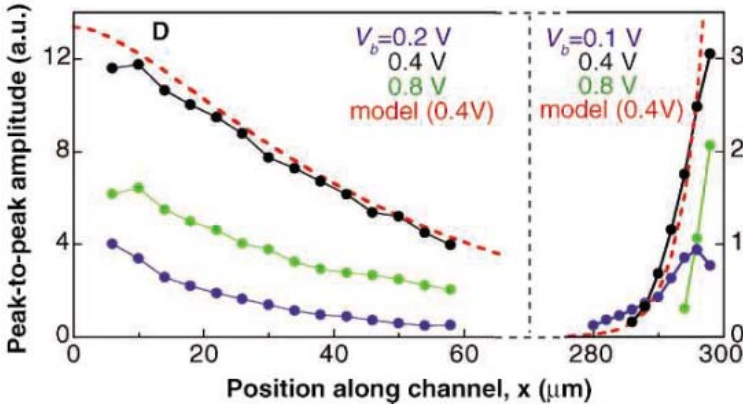


Fig. 3. (**A**) $\theta_K(B_y)$ curves due to injected spins, measured at x_0 = 65 μm from the source contact, for both directions of Fe magnetization **M**. The solid line is a model based on Eq. 1. (**B**) $\theta_K(B_y)$ data acquired at increasing distance from the source contact, showing electrical spin injection persisting out to 120 μm in the *n*-GaAs channel. V_b = +0.4 V. (**C**) Same as (B), but measured at 2-μm increments from the drain contact. (**D**) The peak-to-peak amplitude of the $\theta_K(B_y)$ curves versus distance from the source and drain contacts, for different biases $+V_b$. The dotted line shows the modeled amplitude from Eq. 1 using V_b = +0.4 V, τ_s = 125 ns, and v_d = 2.8 × 10^4 cm/s.

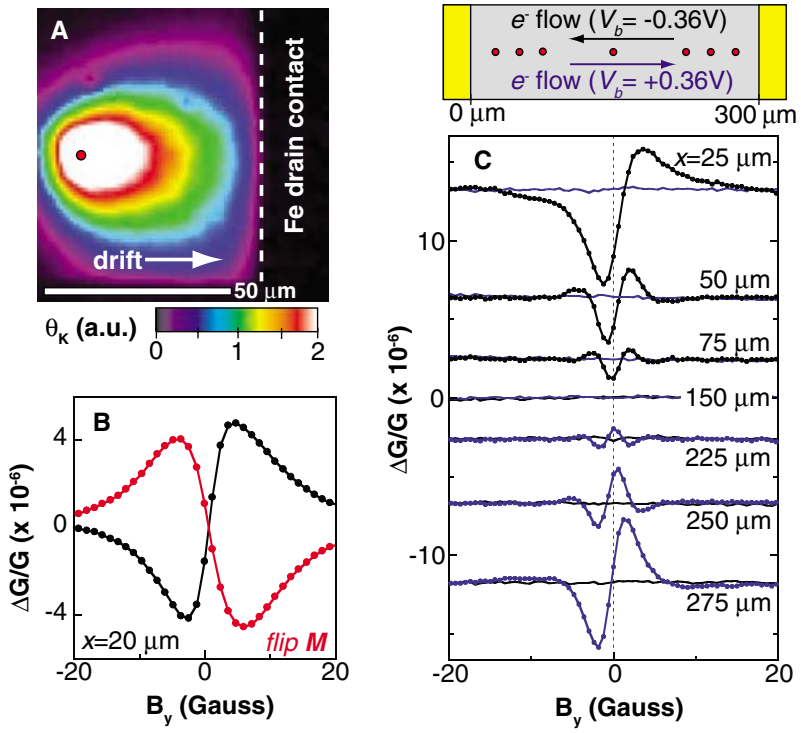


Fig. 4. (**A**) Image of θ_K, showing optically injected electrons, spin polarized along $+\hat{z}$, flowing into the drain contact (V_b = +0.36 V, B_y = 0). (**B**) Normalized conductance modulation $\Delta G/G$ versus B_y for both orientations of Fe magnetization **M**. The high-conductance state occurs when spins flowing through drain are polarized parallel to **M** and the low conductance state occurs when they are antiparallel. (**C**) $\Delta G/G$ versus B_y, for V_b = ±0.36 V, due to spin-polarized optical injection at the positions indicated.

The amplitudes of the $\theta_K(B_y)$ curves near the source and drain contacts are plotted in Fig. 3D for three bias voltages. The exponential decay length for injected spins increases with bias, from ~20 μm at V_b = 0.2 V to ~50 μm at V_b = 0.8 V, as electrons flow more quickly down the channel. In contrast, the accumulated spin polarization extends nearly one spin diffusion length (~10 μm) from the drain at low bias, but this length scale decreases to only a few μm at high bias, because polarized electrons can no longer diffuse backstream against the drift current (*25*). The dotted lines simulate the amplitude decay, using Eq. 1. Experimental $\theta_K(B_y)$ curves with increasing bias from 50 mV to 1.0 V are shown in fig. S3.

Finally, we show that the Fe/GaAs tunnel barriers also function as spin detectors. We optically inject spin-polarized electrons into the *n*-GaAs channel by using a weak laser beam (785 nm, 50 μW) focused to a 4-μm spot. Under bias, these polarized electrons flow into the drain contact (Fig. 4A). The laser polarization is modulated from right- to left-circular (injecting spins along $\pm\hat{z}$) at 50 kHz. The spins precess about B_y as they drift, arriving at the drain with some spin polarization parallel or antiparallel to **M**, depending on the injected spin orientation. We measure the corresponding modulation in the conductance, ΔG, as a function of B_y (*26*–*28*). The spin drift-diffusion equations apply equally well here, and the $\Delta G(B_y)$ curves (Fig. 4B) therefore resemble the $\theta_K(B_y)$ data discussed above. The high-conductance state occurs when the spins flowing through the drain contact are polarized parallel to **M**. This result is consistent with an accumulated (reflected) spin polarization that is antiparallel to **M**. In Fig. 4C, $\Delta G(B_y)$ is shown for both positive

(blue) and negative (black) bias at different injection positions along the channel. Both the amplitude and width of the curves decrease with increasing distance from the drain contact, similar to the previous $\theta_K(B_y)$ data. These data provide conclusive evidence that the Fe/GaAs Schottky tunnel barriers in lateral devices function as both spin detectors and injectors.

These measurements provide a detailed picture of spin transport in simple ferromagnet/semiconductor lateral structures. Smaller lateral dimensions and additional components, including a means to switch the source and drain contacts independently, will enhance the functionality of these devices. Although developing a purely electrical spin-transport device using a field effect or other means for spin manipulation remains a great challenge (*29*), the integration of an electrical injector and detector in a lateral structure represents an important step toward this goal.

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Figs. S1 to S3

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Embedded Nanostructures Revealed in Three Dimensions

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Nanotechnology creates a new challenge for materials characterization because device properties now depend on size and shape as much as they depend on the traditional parameters of structure and composition. Here we show that Z-contrast tomography in the scanning transmission electron microscope has been developed to determine the complete three-dimensional size and shape of embedded structures with a resolution of approximately 1 cubic nanometer. The results from a tin/silicon quantum dot system show that the positions of the quantum dots and their size, shape, structure, and formation mechanism can be determined directly. These methods are applicable to any system, providing a unique and versatile three-dimensional visualization tool.

The past decade has seen device technology enter the realm of nanoscale engineering for a large number of different applications. Many applications involve nanostructures that are embedded in other materials, where it is the size, shape, composition, and chemical interaction with the matrix that are key in determining the overall functionality of the device. Site-specific quantum-dot markers in live cells (*1*), inorganic nanostructures within self-assembled organic or biological templates (*2*), semiconductor nanocrystals (*3*) and metal tips grown on quantum rods and tetrapods (*4*), and catalytic growth of nanowires and nanostructures (*5*) are just some examples of new systems where the size, shape, and location (interaction) of the nanostructures are the critical parameters.

Transmission electron microscopy (TEM) and its variants have given us insight into nanoscale materials issues for over half a century. However, the vast majority of previous studies have made use of the periodicity of the sample (crystal structure) in the direction of the beam propagation, and they only involved the recording of a single two-dimensional (2D) projection (image) to understand the relationships between the structure and its properties. In nanostructures, the periodicity of the crystal structure in the beam direction does not continue indefinitely, and in fact, exactly when and how the periodicity terminates determines the material's properties. In such a case, a single 2D projection of the 3D object can at best give only partial information, and at worst be very misleading. Overcoming the ambiguity in the interpretation of a single 2D projection has been the driving force behind the very recent development of electron tomography that allows materials to be studied in 3D.

The conventional method to study structures with TEM is through high-resolution phase-contrast imaging (*6*, *7*). However, the relatively new technique of scanning transmission electron microscopy (STEM) can be superior to conventional TEM for some materials applications because of the incoherent nature of the imaging, the sensitivity to the atomic number Z of the species in the samples (Z-contrast imaging), direct interpretability, and the possibility of concurrent spectroscopy on the atomic scale (*8*–*12*). In general, electron tomography using Z-contrast imaging in a STEM is the most useful way to study crystalline inorganic nanomaterials in 3D. The reason is that diffraction contrast, which is seen in many bright-field and dark-field TEM images, violates the projection requirement, which states that the signal used for tomographic reconstructions must be a monotonic function of a physical property (*13*). The projection requirement must be fulfilled for a successful 3D reconstruction of the object from the series of 2D tilt images.

We used STEM tomography to study tin-rich (Sn) quantum dots embedded in a silicon

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(Si) matrix with a resolution of ~1 nm^3. Quantum dots are important nanostructures for optoelectronic devices that exploit quantum confinement for discrete energy levels in the dot with a bandgap smaller than the matrix (*14*–*16*). For correct device functionality, the 3D size, shape, distribution, and composition of all the dots must be uniform. It has been shown that Sn_xSi_{1-x} alloy layers with $x \leq 0.1$ grown on Si (100) form α-Sn quantum dots (*17*–*19*). In order for this alloying to take place, Si atoms from the surrounding matrix must diffuse into the Sn layer. This in turn creates vacancies in the Si, which group together to form voids (*20*, *21*). These voids have been shown to have a distinct equilibrium shape, namely a truncated octahedron, or a tetrakaidecahedron (*22*). Previous 2D EM studies (*18*, *19*) have shown that the α-Sn dots also exhibit this faceted shape in the embedded layer (formed by phase separation). This is perhaps not so surprising because α-Sn and Si have the same cubic crystal structure and therefore the same equilibrium shape. However, dots of apparently the same morphology were also observed to form outside of the embedded layers, but the mechanism for such growth could not be identified. In-situ heating experiments (*18*) showed that Sn diffused out of the embedded layer and into the Si voids that were formed due to strain during the growth process (*18*, *19*), thus creating the out-of-layer quantum dots.

Electron tomography was performed on an FEI Tecnai F20 electron microscope (FEI, Eindhaven, Netherlands) at an accelerating voltage of 200 kV at the University of Cambridge. 149 Z-contrast tilt images were taken every 1° over the tilt range of –74° to +74°. The reconstructions were performed using Inspect 3D software [reconstruction techniques described in (*13*)] and visualized using Amira. Figure 1A shows a single image from the series at 0° tilt. Figure 1B shows the tomographic reconstruction of this tilt series, and by comparing the two figures, it is clear that the dots are in the same position and are the same size in projection, indicating a good reconstruction. Figure 1C is the perpendicular projection of the reconstruction, showing that this volume of material actually consists of two layers of quantum dots, with one small dot above the bottom layer, indicated by an arrow. This small dot between the layers is of particular interest because it provides evidence of how the Sn fills the Si voids. The apparently agglomerated dots seen below the layer were not studied, because they are close to the surface and may have transformed into a different phase because of their interaction with the air, or they may have been damaged from specimen preparation techniques. To enable a better view of the small dot between the layers, a second reconstruction was performed incorporating only the small volume surrounding the out-of-layer quantum dot at a far higher spatial resolution. Figure 1, D and E, shows this reconstruction in (001) plan view and (110) cross section, respectively. These panels demonstrate that there are clear facets on all the quantum dots (movie S1), and that although most of them appear to have the same equi-sized shape, there are a number that appear elongated along perpendicular crystal dimensions (see later discussion of this phenomenon).

To have a basis with which to analyze the out-of-layer dot, we first examined one that is in the layer, approximately 7 nm in diameter. Figure 2, A and B, shows the reconstruction of this quantum dot in the (100) and (110) orientations. The insets show the same image with a superimposed outline of a perfect tetrakaidecahedron in those respective orientations. It can be seen from the figures, the insets, and movie S2 that this dot is of uniform width in 3D and fits the assumed truncated octahedron shape proposed from the 2D analysis. Figure 2, C and D, shows the out-of-layer dot, approximately 3.5 nm in diameter. By looking at the projections of the reconstruction of this dot in the (100) and (110) orientations and movie S3, we can see that this dot is not as uniform as are the in-layer dots. Some of the dot is missing in the upper left corner of the overlaid structure (Fig. 2C, inset) and the dot has filled less of the right side of the overlaid structure compared with the left (Fig. 2D, inset). This evidence suggests that the voids are being filled by Sn from one side.

This type of filling is identical to that which has been observed previously for metal precipitates and voids of similar sizes (*23*, *24*).

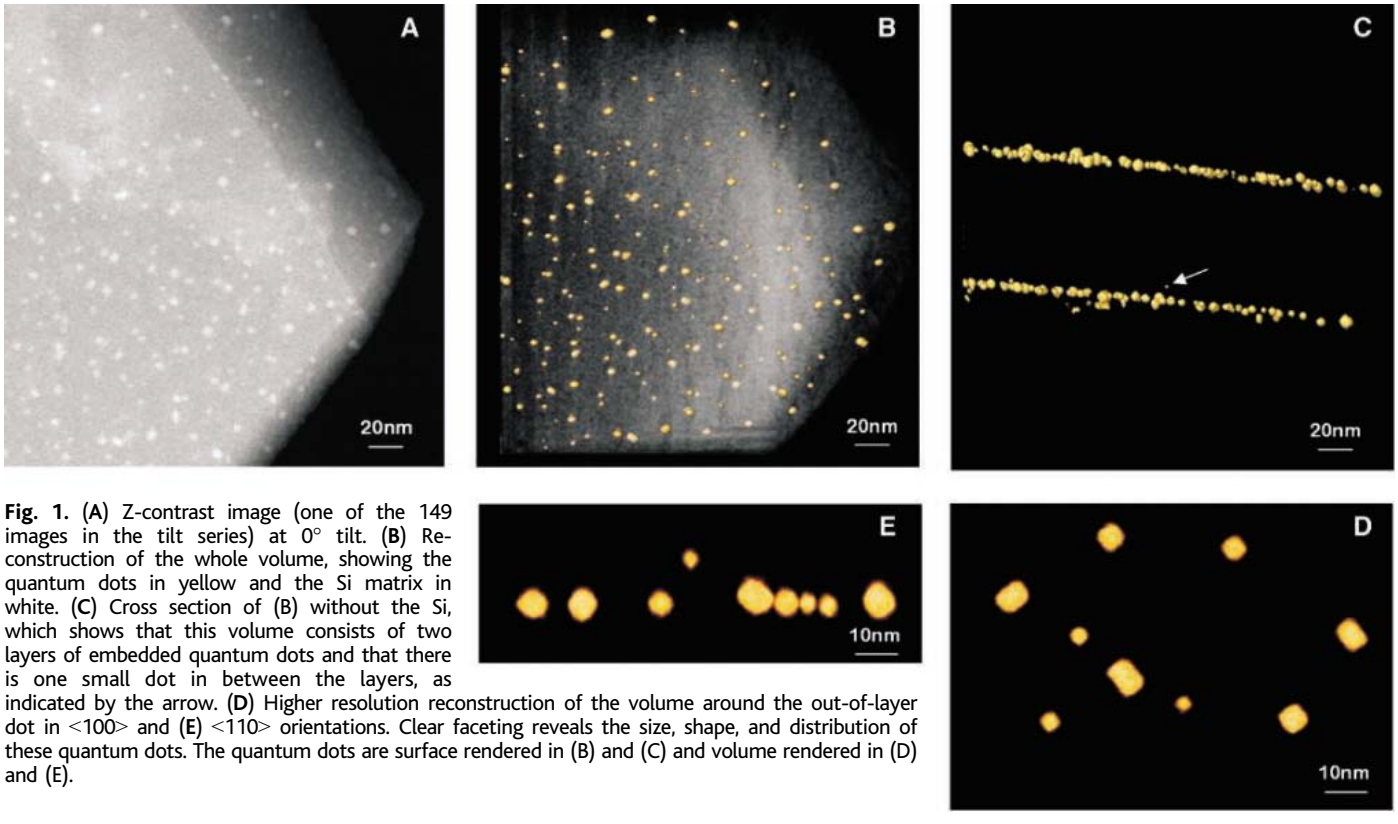

Fig. 1. (**A**) Z-contrast image (one of the 149 images in the tilt series) at 0° tilt. (**B**) Reconstruction of the whole volume, showing the quantum dots in yellow and the Si matrix in white. (**C**) Cross section of (B) without the Si, which shows that this volume consists of two layers of embedded quantum dots and that there is one small dot in between the layers, as indicated by the arrow. (**D**) Higher resolution reconstruction of the volume around the out-of-layer dot in <100> and (**E**) <110> orientations. Clear faceting reveals the size, shape, and distribution of these quantum dots. The quantum dots are surface rendered in (B) and (C) and volume rendered in (D) and (E).

Whereas the bonding in metals and semiconductors is different (metallic versus covalent), the similarities in the formation mechanism indicate that the shape and size of embedded nanostructures may be driven by the same mechanism for all systems. Rich *et. al*. (*25*) studied monolayer growth of Sn on Si (100) and found that after ~1.5 monolayers of deposition, the growth becomes 3D, forming clusters that then coalesce. From high-resolution synchrotron photoemission spectra, they were able to deduce that there are two distinct adsorption sites of Sn on Si (100), called S1 and S2. For coverages between 0 to 0.2 monolayers, the S1 sites dominate; for coverages between 0.2 to 0.68 monolayers, the S1 and S2 site populations are nearly equal; and for coverages above 1 monolayer, the S1 sites dominate again. It is believed that the S2 sites lie below the S1 sites, with the Sn atoms preferentially replacing the surface Si atoms located in a dimerized layer, whereas the S1 sites are dispersed on the surface, bonding to two Si surface atoms equivalently. The domination of these surface sites at coverages beyond 1 monolayer indicates a path for the initiation of the 3D growth observed. Similar results have been found for Sn on Si (111) with spectroscopic measurements (*26*), as well as direct scanning tunneling microscopy imaging showing the formation of 3D α-Sn islands on the Si (111) surface (*27*). Experiments have pointed to three distinct growth modes: layer-by-layer Frank–Van der Merwe growth; 3D nucleation upon contact, called Volmer-Weber growth; and Stranski-Krastonov growth, in which a few monolayers are adsorbed layer-by-layer before a transition to 3D growth (*24*). Based on our findings and those in (*24*–*27*), it appears that the system described here follows Stranski-Krastonov growth. The initial monolayer growth that wets the surface of the void is not resolved in the tomographic reconstruction, but the high-resolution Z-contrast images in (*18*) hint at this with slightly higher contrast around the edges of the quantum dot. However, the subsequent 3D growth is consistent with the observations presented here, because we see the void being filled from one side, indicating there has been 3D nucleation of the Sn inside the void that would then propagate until it reaches the other side.

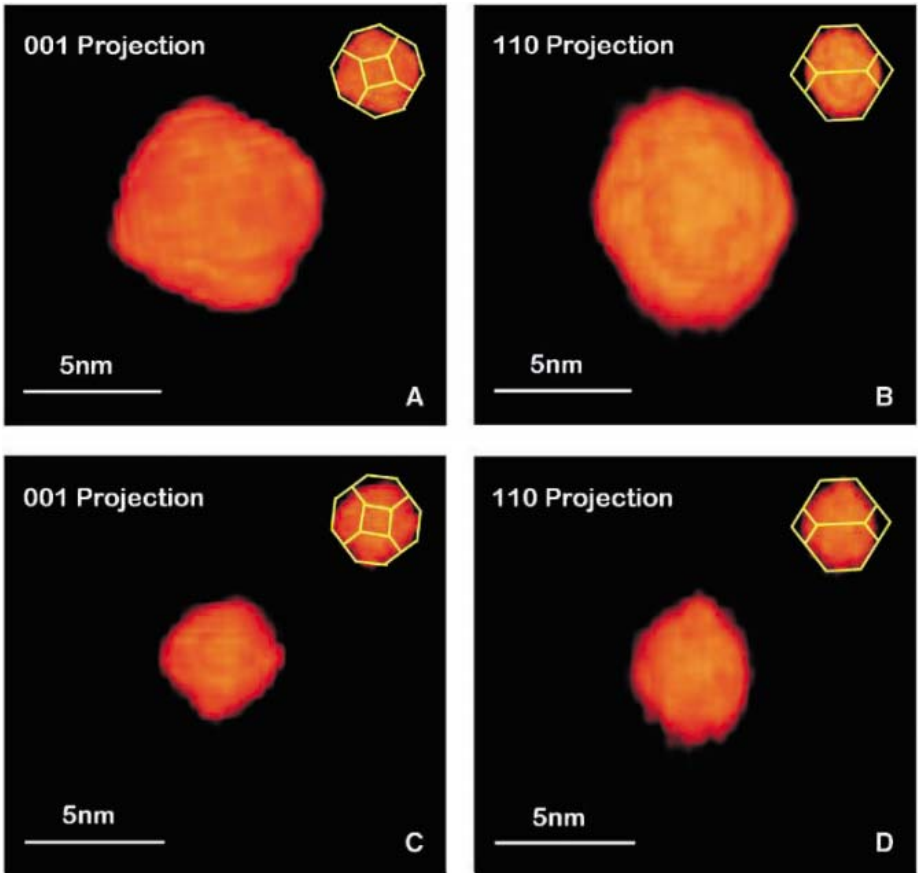

Fig. 2. (**A**) A reconstruction of a 7-nm in-layer quantum dot in plan view, with an inset showing good agreement with the truncated octahedron shape. (**B**) The same dot in cross section, again with good agreement. (**C** and **D**) present the out-of-layer 3.5-nm quantum dot and show that this dot is not uniform, but is formed by filling a void in Si from one side to the other. The quantum dots in this figure are all volume rendered.

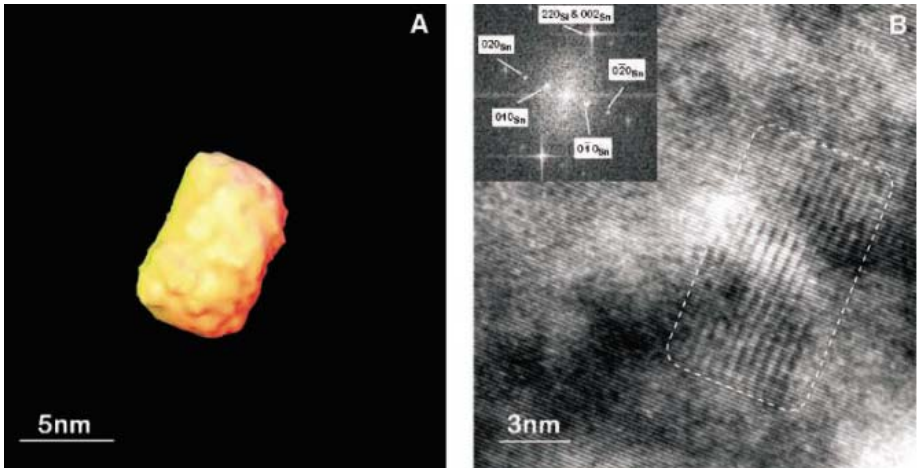

Fig. 3. (**A**) Surface rendered reconstruction of a β-Sn dot showing a clear elongation of the dot. The fine scale surface roughness here is an artifact of the reconstruction process. (**B**) High-resolution TEM image with a fast Fourier transform inset, showing that these β-Sn dots have a different crystal structure than that of α-Sn (the β-Sn dot is outlined in a dashed line). The coherent interface at which growth is fastest is the interface between $(220)_{Si}$ and $(020)_{\beta\text{-}Sn}$.

A number of dots in this volume appear elongated in one direction (Fig. 1, D and E). Figure 3A and movie S4 show a reconstruction of one such dot, which has the appearance of a rectangular parallelepiped rather than an octahedron. The difference in size and shape of these dots implies that a different phase is present (β-Sn is the stable phase at room temperature). The presence of β-Sn was confirmed with conventional high-resolution TEM, and Fig. 3B shows a lattice image of one such dot. The rectangular projection is revealed, and a Fourier transform of the dot (Fig. 3B, inset) confirms that the crystal structure is different from the face-centered cubic α-Sn structure. It appears that beyond a critical diameter of ~8 nm, the α-Sn quantum dots are no longer the energetically favorable structure, and they transform into β-Sn. The 3D reconstructions are the only way to verify the nature of this transformation. From Fig. 3, A and B, it is clear that the transformation leads to an elongation of the Sn dot in one of the in-plane $<110>_{Si}$ directions and in particular, the development of

a favored interface between the β-Sn and the (110) planes in the Si matrix. The excellent lattice match between the (100) planes of the β-Sn and the (110) Si is clearly the driving force for this elongation, leading to an extended coherent interface. Symmetry allows an equivalent elongation in the perpendicular in-plane $<110>_{Si}$ direction (Fig. 1D).

High-resolution Z-contrast tomography in the STEM was used to elucidate the formation mechanism of embedded quantum dots. We have identified embedded quantum dots with both the α-Sn and β-Sn phases, with a transformation into β-Sn beyond a critical diameter of ~8 nm. Some quantum dots are formed outside the embedded layers due to diffusion of Sn from the layers to fill Si voids. These dots are formed by Stranski-Krastonov growth, filling from one side of the void to the other after an initial wetting of the surface of ~1 to 2 monolayers. These results demonstrate that STEM tomography can directly determine the location, size, shape, structure, and formation mechanism of embedded nanostructures in 3D with a resolution of 1 nm^3, which is essential information for all of the nanosciences.

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Colloidal Jamming at Interfaces: A Route to Fluid-Bicontinuous Gels

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Colloidal particles or nanoparticles, with equal affinity for two fluids, are known to adsorb irreversibly to the fluid-fluid interface. We present large-scale computer simulations of the demixing of a binary solvent containing such particles. The newly formed interface sequesters the colloidal particles; as the interface coarsens, the particles are forced into close contact by interfacial tension. Coarsening is markedly curtailed, and the jammed colloidal layer seemingly enters a glassy state, creating a multiply connected, solidlike film in three dimensions. The resulting gel contains percolating domains of both fluids, with possible uses as, for example, a microreaction medium.

The search for new materials with mesoscale or nanoscale structure is a major theme of current physical science. Routes that exploit spontaneous self-assembly in thermal equilibrium are important (*1*, *2*), but nonequilibrium processes offer more control—because assembly is then governed not just by thermodynamic conditions but by the entire process history [e.g., (*3*–*5*)]. Moreover, the resulting materials may become trapped in deeply metastable states such as colloidal clusters, glasses, and gels (*3*, *5*–*7*), remaining more robust than an equilibrium phase to subsequent changes in thermodynamic conditions. This is a key consideration in determining the shelf-life and flow behavior of everyday products such as paint, vaccines, and yogurt.

We use computer simulations to explore a kinetic pathway that leads to the creation of amorphous soft-solid materials. In such a material, which we call a bicontinuous interfacially jammed emulsion gel (or Bijel) (*8*), a pair of interpenetrating, bicontinuous fluid domains are frozen into a permanent arrangement by a densely jammed monolayer of colloidal particles at the fluid-fluid interface. Such materials may have distinctive properties, stemming directly from the nonequilibrium, arrested nature of the monolayer: Bijels should be highly tunable in elasticity and pore size through the volume fraction ϕ and radius a of the solid particles. (The radius can be varied from micrometers to nanometers without altering the physics of structure formation by the route reported here.) One possible application, explored below, is as a cross-flow microreaction medium in which two immiscible fluids are continuously brought into intimate contact by pumping them in opposite directions through a static Bijel.

To achieve maximal stability of a particle-laden interface, the colloidal particles should be chosen with nearly equal affinity for the two liquids involved (*9*). This creates similar values for the two fluid-solid interfacial tensions, and thus a fluid-fluid-solid contact angle close to 90° (known as neutral wetting). A spherical particle is then in stable equilibrium, with its equator positioned at the fluid-fluid interface. In practice, this equilibrium is so stable that detachment of such a particle cannot be achieved by thermal motion alone (*9*). For neutral wetting, the fluid-solid interfaces have the same total energy regardless of particle position, but the fluid-fluid interfacial area is reduced, by a disk of radius a, when the particle lies midway across the interface. The detachment energy ε is the interfacial energy of this disk, $\varepsilon = \sigma\pi a^2$, with σ the fluid-fluid interfacial tension. Hence $\varepsilon/k_BT = (a/a_0)^2$, where $a_0^2 = k_BT/\pi\sigma$ (k_B is the Boltzmann constant and T is temperature). For T = 300 K and σ typically ~0.01 Nm^{-1} or larger, a_0 is 0.4 nm or less. Thus, $\varepsilon/k_BT \geq 10$ even for a particle of 1 nm radius, and

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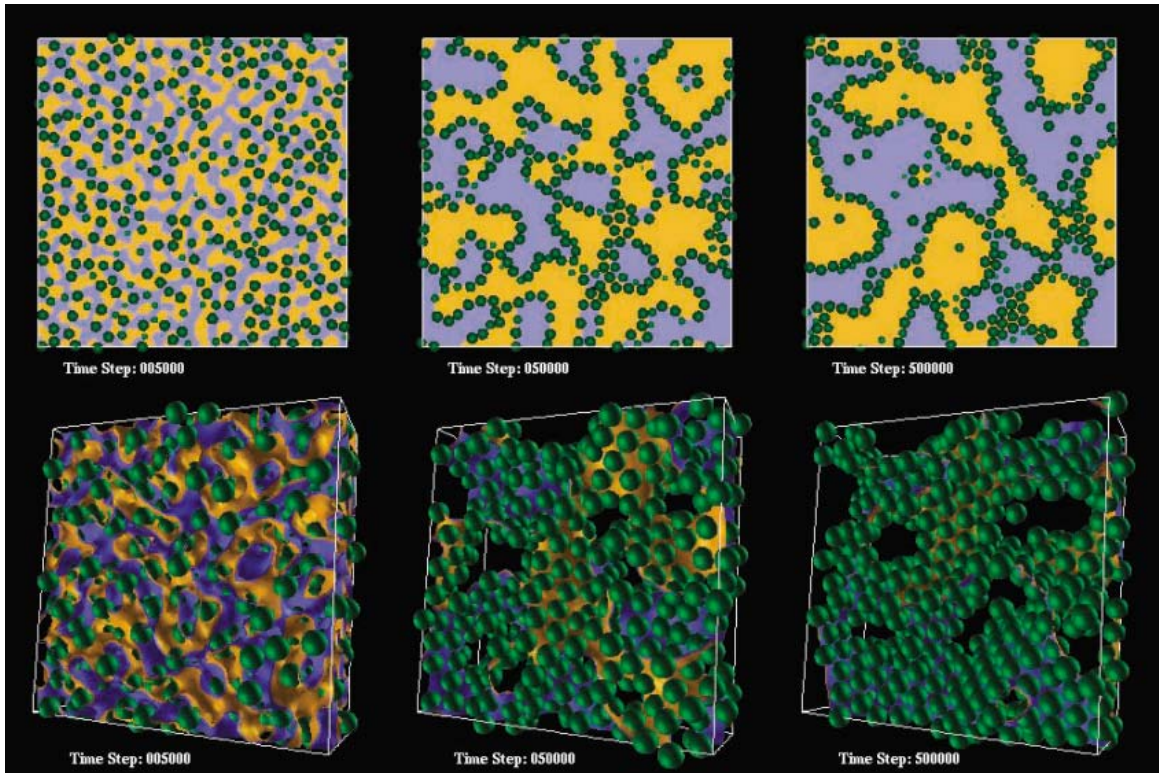

Fig. 1. Time evolution of monodisperse neutrally wetting colloidal particles at volume fraction $\phi = 0.2$ in a binary solvent following a quench. (Upper panels) A 128×128 section through the full simulation (performed on 128^3 lattice) is shown. The two fluids are colored yellow and blue. Monodisperse colloidal particles (green) are shown only if overlapping the plane of the section, with parts lying behind this plane occluded (so that particles whose midpoint is behind the plane appear reduced in size). Sequestration of the particles, followed by near-arrest of the bicontinuous structure, is seen. Frames are at 5000, 50,000, 500,000 LB time steps; for parameter details see (*12*). (Lower panels) A three-dimensional (3D) view of a $64 \times 64 \times 24$ piece cropped from the same simulation with the same time frames. Both fluids are now shown transparent with the two sides of the fluid-fluid interface painted yellow and blue. Sequestration, arrest, and fluid bicontinuity of the resulting structure are all apparent.

thermally activated detachment can be safely neglected for, say, $a \geq 3$ nm.

We consider near-neutral wetting particles suspended in a binary solvent under conditions where the fluids are fully miscible (generally at high temperature) and of roughly equal volume fraction. In the absence of strong attractions between them, the particles will diffuse freely. If the temperature is quenched deep into a two-phase region, the solvents will demix by spinodal decomposition (*10*). A sharp interface between the two fluids develops, and coarsens. During the coarsening, which is driven by the tendency of the interface to reduce its area, the characteristic length scale $L(t)$ initially increases with time in a well-understood manner (*11*), causing bumps on the interface to flatten and necks between neighboring domains of the same fluid to pinch off.

We have studied what happens after this initial separation by simulations (*12*) using the lattice Boltzmann (LB) method (*13*–*17*). We find that, as coarsening proceeds, the interface sweeps through the fluid phases, efficiently collecting and sequestering the colloidal particles. Initially, the attached particles have little effect on the interfacial motion, but as more are collected and the interfacial area shrinks, they soon approach a densely packed monolayer. At this point, the fluid must either (i) stop coarsening at some length scale $L(t) = L^*$ or (ii) thereafter expel particles steadily from the ever-shrinking interface. In our simulations, we see a drastic curtailment of the coarsening and very little particle expulsion. This suggests that the free-energy landscape of the dense colloidal film is such as to trap particles on the interface in a metastable, amorphous state (*18*).

Figure 1 shows the structure as time evolves; for visibility, only a small part [in cross section (upper panels) or crop (lower panels)] of the full system is shown. Movie S1 shows an animation of the observed sequence of events within the cropped region of Fig. 1; this clearly shows the particle sweep-up and the pronounced slow-down of coarsening. Movie S2 shows the entire simulation domain for another run, in which bidisperse particles are used; this prevents development of any local crystalline order in the interfacial colloid layer (arguably visible in Fig. 1). Movie S3 shows a similar subregion for this case as in Movie S1. The results are qualitatively the same; see Fig. 2 for a snapshot at late times. Figure 3 shows the time dependence of the domain size $L(t)$ in each case.

The parameter values chosen for these simulations (*12*) map onto particles of radius $a = 5$ nm in a symmetric pair of fluids each having viscosity $\eta = 10^{-3}$ Pa s and mass density $\rho = 10^3$ kg m^{-3}, with $\sigma = 6 \times 10^{-2}$ N m^{-1} at $T = 300$ K; such values are typical of a short-chain hydrocarbon/water or alcohol/water mixture. Our particles have purely repulsive interactions, with a range extending somewhat beyond their hard-sphere (hydrodynamic) radii (*12*), so that particles remain visibly separated even in a dense monolayer. The parameter mapping is made by matching dimensionless control groups ε/k_BT and $a\rho\sigma/\eta^2$ (*12*, *19*). Brownian motion of the colloidal particles is included (*12*), but has rather little effect during the time regime we can reach by simulation (see below), and would have even less effect with larger particles. We have also checked the role of short-range, thermally reversible bonding among colloids (*7*), but this too has little effect. These observations are attributable to the strong separation between Brownian and interfacial energy scales referred to above.

A number of numerical compromises were made to keep the simulations tractable (*12*). First, the Reynolds number $Re = (dL/dt)\rho a/\eta$ is much larger than in the real system, though we still have $Re \ll 1$ (*19*). Second, the scale separation between the particle radius a and the fluid-fluid interfacial thickness ξ is only modest (a factor of 2 or 3), with the lattice spacing, in turn, not much less than ξ. This gives imperfect discretization of the fluid-fluid interface around particles and may underrepresent the energy barrier to short-scale rearrangements (*12*). Finally, for the physical parameters given above, the effective run-time of our largest simulations is about 300 ns. (For larger particles, say $a = 3$ μm, the equivalent run time would be around 5 ms.)

Although these simulations dramatically confirm our proposed kinetic pathway for creating a fluid-bicontinuous state with a particle-laden interface, they cannot tell us whether this state

is a fully arrested gel on laboratory time scales. Unlike our simulations, the latter vastly exceeds the time scale $\tau = 6\pi\eta a^3/k_BT$ characterizing Brownian motion of colloids. Nonetheless, the observed behavior, particularly for bidisperse particles, is consistent with that of a long-lived, metastable, arrested state. In common with other such states (including colloidal glasses), Bijels might show slow aging behavior as the interface approaches saturation. This may explain the residual late-time dynamics visible in the $L(t)$ curves of Fig. 3. Alongside aging, the slow residual dynamics could be due to the incomplete separation of length scales in LB noted above or, in the monodisperse case, due to a tendency for the interfacial layer slowly to acquire local crystalline order. (Such ordering would not preclude, and might even enhance, eventual structural arrest.) We have also assessed the particle mobility in the interfacial film by measuring the distribution of individual particle displacements at late times. We found this to be dominated by the residual relaxation dynamics of the structure rather than by diffusion within the film.

The near-complete cessation of fluid motion on time scales on the order of τ suggests that further coarsening, which requires expulsion of particles from the interface, cannot take place without colloidal Brownian motion. If, as argued earlier, such motion is ineffective at detaching particles from a static interface, coarsening must cease altogether. In principle, lateral diffusion within a film of fixed area might continue. However, the surface pressure of such a film is estimated (*20*) as $\Pi \sim k_BT/[a^2(\psi_m - \psi)]$, where ψ is the areal fraction and ψ_m that of a maximally close-packed configuration. For this pressure to balance the interfacial tension requires that $\psi_m - \psi \sim (a_0/a)^2$. For large enough particles, this ensures that ψ exceeds any threshold value, so long as this value is less than ψ_m, for the onset of an arrested state within the film.

Further evidence for interfacial arrest was gained by additional, higher-resolution simulations that examine the dynamics of two specific structural motifs characteristic of the bicontinuous structure. One of these is a long cylinder, representing a fluid neck. Without particles the Rayleigh-Plateau instability (*21*) would cause the cylinder to break into droplets. We show in fig. S1 a dense bidisperse colloidal packing on a cylindrical interface. When perturbed, this structure shows no sign of either ordering or breakage, and the initial undulation visibly decays, rather than grows. The structure then arrests, and remains unchanged for the duration of the simulation, which is 10 times as long as the time-to-rupture of an unprotected cylinder. Our second structural motif is a periodically rippled surface, whose bumps are broadly characteristic of a non-necklike section of the bicontinuous interface between fluids. Without particles, the ripple would rapidly be pulled flat by interfacial tension. Figure S2 shows how this process is interrupted by interfacial jamming. After an initial transient decay, the film jams, and bumps on it persist at least 30 times as long as the decay time without particles. There is negligible macroscopic motion during the latter half of this simulation.

These results show that, at sufficient interfacial coverage (*22*), both necks and bumps can arrest by jamming of the adsorbed colloidal layer into a densely packed, and therefore presumably glasslike, state. Because these two structural elements are, in combination, the driving features of bicontinuous coarsening (*21*), their arrest would be enough to prevent coarsening. Hence these studies provide very strong supporting evidence for an eventual arrest of our bicontinuous structure, caused by a jamming transition (*23*) within the colloidal monolayer. This transition is induced by the (capillary) stresses arising from the fluid-fluid tension.

Once the interfacial film has fully arrested, because it percolates in three dimensions, the entire material will acquire solid elasticity at scales beyond L^*. The static modulus G of the resulting gel should scale with the interfacial energy density σ/L; so long as nearly all particles end up on the interface, $L^* \sim a/\phi$ with ϕ the particle volume fraction. For $\sigma = 0.01$ N m^{-1}, $0.01 \leq \phi \leq 0.1$, and 5 nm $< a <$ 5 μm, we estimate $20 \leq G \leq 2 \times 10^5$ Pa. This is a very wide "tuning" range for material design. Under nonlinear stress the interfacial area will dilate substantially; only a modest dilation (say 10%) may suffice to cause melting of the particle layer and drastic fluidization. This might instigate both flow and coarsening above some yield stress $Y \cong 0.1\ G$. If the stress falls back below Y, we expect resolidification, possibly with remanent anisotropy (hysteresis). The nonlinear flow behavior of these gels could thus show a remarkable strain-melting, possibly reminsicent of a colloidal glass, but with a much higher stress scale set by interfacial, not Brownian, forces. The estimates above for the material properties of the gel stem from the jamming of colloids by the interfacial forces

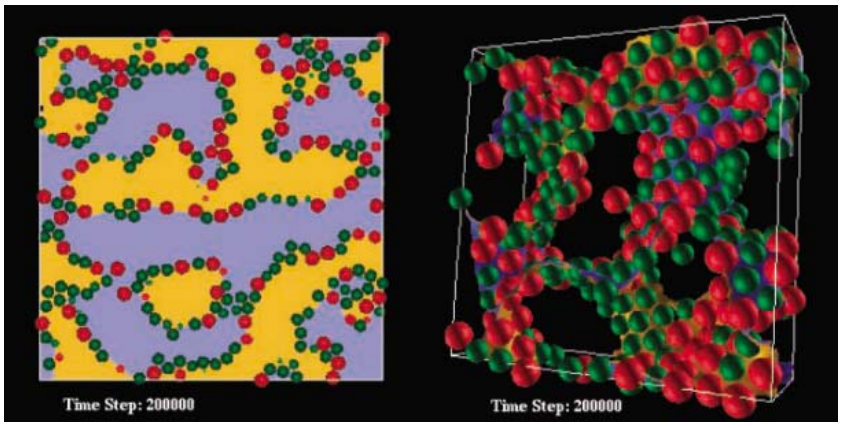

Fig. 2. Structure at 200,000 time steps in a simulation of bidisperse neutrally wetting particles in a binary solvent following a quench, in section and 3D view. Color coding as in Fig. 1 but with larger particles shown in red; size ratio, 1.2:1. (**Left**) A 128 × 128 section; the top left quadrant of this square is coincident with the front face of the 64 × 64 × 24 cuboid used for the 3D view (**right**). There is no sign of local crystalline order in the particle film (visible in Fig. 1, lower panels), although some tendency toward local segregation by particle size is seen. For parameter details see (*12*). The same structure, evolved to 590,000 time steps, is shown in Fig. 4.

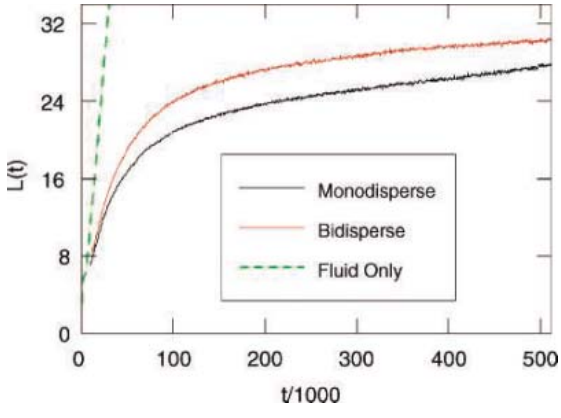

Fig. 3. Time evolution of the structural length scale $L(t)$ for monodisperse (lower curve) and bidisperse (upper curve) particle runs as described in (*12*). L is measured in units of the LB lattice and t in LB time steps. Without particles, coarsening would proceed with the slope indicated by the dotted line (*11*). Near-arrest is visible, suggesting a finite asymptotic domain size L^*, particularly in the bidisperse case. This L^* is less than a quarter of the simulation box size and not limited by finite-size effects (*11*). For the parameter values chosen (corresponding to 5-nm particles), the data shown run approximately from 6 to 300 ns in real time (*12*), with $L^* \cong 70$ nm. (At times less than 6 ns, the fluids are demixing diffusively so that sharp interfaces have not yet formed.)

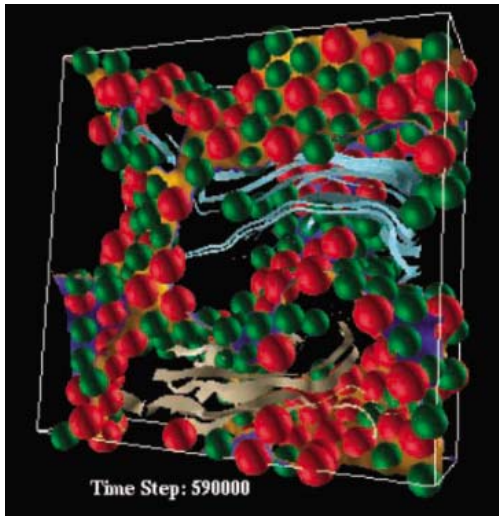

Fig. 4. A $64^2 \times 24$ section of the near-arrested bicontinuous structure in the run of Fig. 2, showing velocity streamlines for the two component fluids under cross-flow forcing with velocity $\sim 0.01\sigma/\eta$ (*12*). The group of beige-colored streamlines starting at the bottom left show flow in one fluid (the yellow side of the interface) moving rightward; the second group (blue) starting on the upper right show flow in the second fluid moving to the left. There is no discernible motion of the interfacial structure at this flow rate.

and apply even for purely repulsive particles. Any additional bonding attraction, if of sufficient strength, might enhance the rigidity of the interfacial layer, but may also cause colloidal aggregation within the bulk phase(s) before monolayer formation (*24*). Fusing the colloids after gel formation (e.g., by irradiation) would completely stabilize the structure and drastically alter the flow behavior.

Our study differs from previous work in which colloidal particles were used to stabilize spherical (*9*, *25*) and aspherical (*24*) emulsion droplets of one liquid in another. Under compression, such emulsions can form robust gel phases with interesting mechanical properties (*26*), but fluid bicontinuity is not among them. The previously preferred route to particle-stabilized emulsions involves agitation of immiscible fluids and does not appear to favor bicontinuity (*9*). Other related work (*6*, *27*–*29*) involves particles with a strong preference for one of the two liquids, creating a particle network within the chosen liquid rather than at the interface.

We expect Bijels to have several interesting physical properties beyond those discussed above. First, the fluid-bicontinuous state should remain equally insoluble on exposure to either of its solvents. This contrasts with particle-stabilized emulsion gels formed by compression (*26*), in which an excess of the continuous phase could cause droplets to separate, losing macroscopic rigidity. In Bijels this will not happen, because neither of the two interpenetrating fluids can alter its volume without also increasing the total interfacial area. The Bijel can thus metastably support simultaneous coexistence with bulk phases of both fluids. This is reminiscent of an equilibrium property of middle-phase microemulsions, which are bicontinuous states with an interface stabilized by amphiphilic molecules (*30*). In contrast to Bijels, such microemulsions are not gel phases, but inviscid fluids, as a result of their high interfacial mobility.

Second, fluid bicontinuity imparts high permeability of the gel to either of its component solvents, and any reagents dissolved in them. Accordingly, Bijels may have potential as media for continuous-process microreactions (*31*, *32*). Specifically, a static gel could support a steady permeation flow of both fluids simultaneously in opposite directions. This would bring two molecular reagents, soluble only in mutually immiscible fluids, into intimate contact at the fluid-fluid interface in the interstitial regions between the colloids. Reaction products soluble in either phase would be swept out continuously. As a test of this concept, Fig. 4 shows a simulation in which the two fluids are moving through the structure in opposite directions. On the time scale of our simulation, the gel has easily enough mechanical integrity to sustain this cross-flow without breaking up. Within the mapping onto physical parameters made previously, the chosen cross-flow fluid velocity $v = 0.01\sigma/\eta$ is ~ 10 cm s^{-1}; this is an extremely large value, given the pore scale L^* of only 70 nm. Local shear rates are $\sim 10^6$ s^{-1}.

In summary, we have presented simulation data showing formation of a self-assembled bicontinuous structure with interfacially sequestered particles. This followed a kinetic pathway involving a colloidal suspension in a binary solvent, initially miscible, that undergoes a temperature quench. Our simulations show a drastic curtailment of coarsening, consistent with eventual structural arrest: a scenario further supported by higher resolution studies of appropriate structural motifs (bumps and necks). This suggests a route to the creation of a new class of gels, Bijels, with potentially distinctive physical properties.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/309/5744/2198/DC1
Materials and Methods
Figs. S1 and S2
References and Notes
Movies S1 to S3

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The Rise of Oxygen over the Past 205 Million Years and the Evolution of Large Placental Mammals

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On the basis of a carbon isotopic record of both marine carbonates and organic matter from the Triassic-Jurassic boundary to the present, we modeled oxygen concentrations over the past 205 million years. Our analysis indicates that atmospheric oxygen approximately doubled over this period, with relatively rapid increases in the early Jurassic and the Eocene. We suggest that the overall increase in oxygen, mediated by the formation of passive continental margins along the Atlantic Ocean during the opening phase of the current Wilson cycle, was a critical factor in the evolution, radiation, and subsequent increase in average size of placental mammals.

It has long been recognized that atmospheric oxygen levels play a key role in the evolution of metazoans (*1*), yet our understanding of precisely how oxygen concentrations influence specific animal evolutionary traits is limited. Although many metazoans are capable of acclimating to hypoxic conditions by lowering metabolic rates and/or operating the tricarboxylic acid cycle partially in reverse (*2*), these physiological modifications cannot be sustained indefinitely. Controls of atmospheric oxygen by the carbon and sulfur cycles (*3*, *4*) have led to models based on analyses of the isotopic composition of carbonates and sulfur (*3*, *5*) or on the relative abundance of different rock types (*6*), which suggest that atmospheric oxygen concentrations varied throughout the Phanerozoic, with a maximum ~300 million years ago (Ma), a minimum ~200 Ma, and an overall rise from ~200 Ma to the present (*5*, *6*). However, the range and underlying causes of these variations in oxygen are not well understood. Here, we provide an isotopic record for organic carbon, which we analyzed in conjunction with isotopic records for carbonates and sulfates for the past 205 million years (My). Our analysis suggests that ambient oxygen levels approximately doubled from ~10% by volume (76 Torr) to 21% (160 Torr) over this period. Concurrent examination of the fossil record suggests that this change in oxygen tension was potentially a key factor leading to the evolution of large placental mammals in the Cenozoic.

On time scales of millions of years, the oxidation state of the atmosphere and surface ocean is determined by the balance of electron equivalents sequestered in the lithosphere relative to that consumed primarily in reactions at Earth's surface (*3*, *5*). In principle, changes in the net electron balance through time can be inferred from the isotopic composition of carbon (carbonates and/or organic matter) and sulfur (sulfate and/or pyrite) sinks; the simultaneous use of both isotopic signatures best constrains the analysis (*7*, *8*).

We determined the isotopic composition of both carbonates (*9*, *10*) and organic matter (this study) from a series of marine sediment cores from the Lower Jurassic through the Cenozoic (Fig. 1). These carbon isotope data are coeval, high-resolution (225,000-year average sampling interval) records from both carbonates and organic matter that cover the past 205 My, providing full constraint on the carbon sinks. Correlations to shorter duration records of transient $\delta^{13}C$ excursions and 3- to 20-My-long $\delta^{13}C$ events establish the global nature of our data set (*10*); here, we focus instead on the 100-My-scale trends. The isotopic data for carbonates reveal a long-term increase in $\delta^{13}C_{carb}$ of 1.1 per mil (‰) from the beginning of the record to ~15 Ma, followed by a sharp reversal amounting to about 2.5‰. Statistical analysis of the regression of the inferred long-term increase (205 to 15 Ma) indicates that the slope is significantly different from zero ($P < 0.05$). Over the same time period, buried organic matter ($\delta^{13}C_{org}$) became depleted in the light isotope by ~5‰. Statistical analysis of this record also reveals a long-term secular trend. The isotopic records of both carbonates and organic carbon require increases in both the extraction of ^{12}C from, and supply of ^{13}C to, the mobile carbon reservoirs through (i) increase in net burial of organic carbon in the lithosphere, with an implied increase in net oxidation of the atmosphere, and (ii) increase in $\delta^{13}C$ signature of carbon introduced to the mobile carbon reservoir from volcanic outgassing and weathering of continental rocks. Sensitivity tests establish that neither factor alone can account for the measured $\delta^{13}C$ changes (*10*, *11*). The long-term depletion of CO_2 associated with greater organic carbon burial may also have been a key factor that selected for the β carboxylation in marine diatoms (*12*) and C_4 photosynthetic pathways in terrestrial plants (*13*, *14*). Indeed, the evolution of these alternative photosynthetic pathways appears to have led to an increase in $\delta^{13}C_{org}$ as ^{13}C-enriched organic matter was buried over the latter half of the Cenozoic and ultimately contributed to the $\delta^{13}C_{carb}$ decrease that began in the mid-Miocene (*10*).

Using three isotopic signatures ($\delta^{13}C_{carb}$, $\delta^{13}C_{org}$, and $\delta^{34}S_{sulf}$), we reconstructed the history of O_2 over the past 205 My by hindcasting from the present value of 21% using the model of Berner (*11*) (Fig. 2). The results suggest that atmospheric O_2 was at a nadir in the Triassic and increased throughout the Mesozoic to approximately 18% of the total atmospheric volume. There appears to have been a relatively large spike in O_2 in the Eocene, when levels may have reached as high as 23%, followed by a small decline over the past 10 My. These results are qualitatively similar to those obtained by Huey and Ward (*15*), with the important difference that our results suggest that the rise in O_2 to contemporary levels was obtained by 50 Ma.

Net oxidation of Earth's surface reservoirs requires a net burial of organic matter and/or pyrite (*5*). Over the past 205 My, the burial efficiency of organic matter in marine sediments was greatly enhanced by the evolution of relatively large, nonmotile phytoplankton taxa, especially coccolithophorids and diatoms (*16*). The radiation and expansion of the latter phytoplankton taxa occurred concurrently with the fragmentation of Pangea, marking the initiation of the current Wilson cycle, and the opening of the Atlantic Ocean basin. The formation of extensive passive continental margins in the circum-Atlantic region has provided a long-term storehouse for organic matter since the early Mesozoic (*10*). Indeed, most of the world's known petroleum reserves originated from the burial of biomass produced by eukaryotic phytoplankton in the Mesozoic and early Cenozoic on continental margins and shallow seas (*17*). The rise in O_2 in the Eocene and Oligocene corresponds to a major radiation of diatoms (*16*), which are responsible for a large fraction of organic carbon buried on continental margins (*18*). The net oxidation of Earth's atmosphere, driven largely by the burial of organic matter in marine sediments along continental margins supplemented by burial

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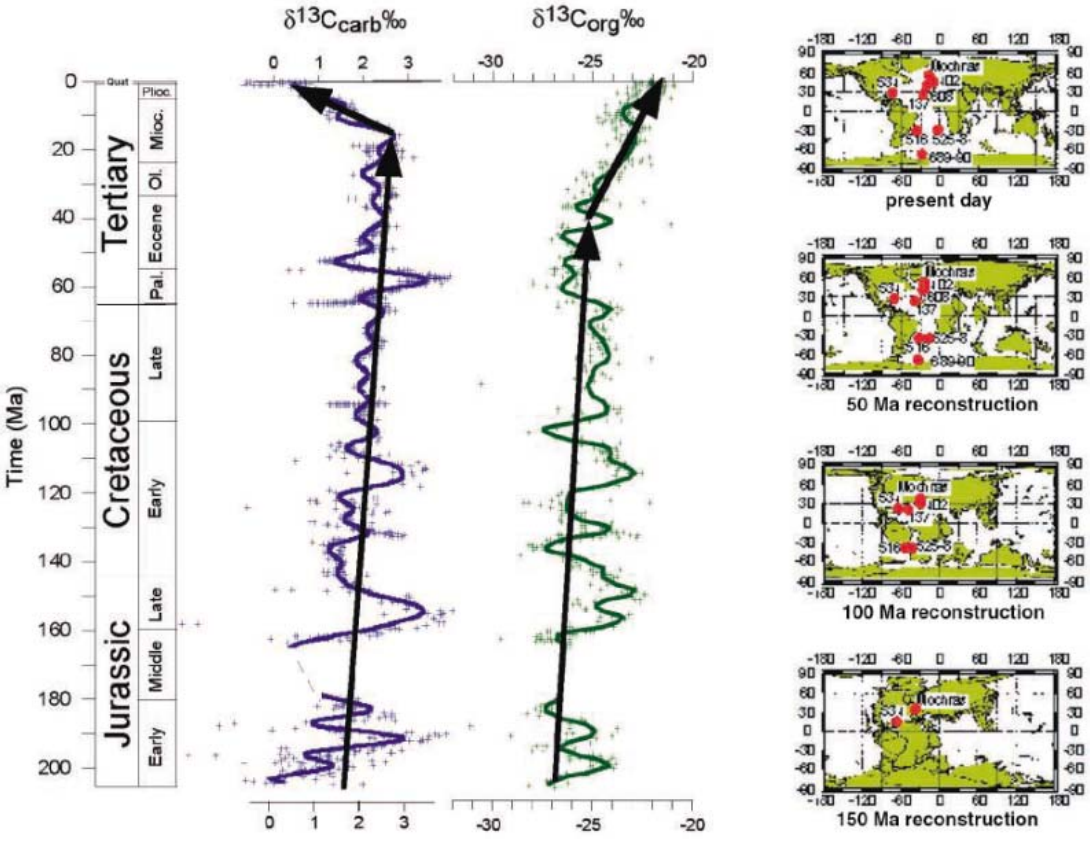

Fig. 1. Composite bulk sediment $\delta^{13}C_{carb}$ (*9*, *10*) and $\delta^{13}C_{org}$ (this study) records for the Jurassic through the Cenozoic. Samples are primarily from open ocean Atlantic Deep Sea Drilling Project (DSDP) and Ocean Drilling Program (ODP) boreholes; the epicontinental Mochras Borehole (Wales) was used for the Lower Jurassic because there is little to no pre-Middle Jurassic ocean floor left. Site locations are shown in a series of paleogeographic reconstructions at 50 My intervals (www.odsn.de/odsn/index.html). We used least-squares regression (95% confidence interval) to determine the long-term trends in $\delta^{13}C$, where x = age and y = $\delta^{13}C$: (i) $\Delta\delta^{13}C_{carb}$ = –2.52‰ for 0 to 15 Ma, y = (0.168 ± 0.024)x + (0.049 ± 0.17), R = 0.89; (ii) $\Delta\delta^{13}C_{carb}$ = 1.1‰ for 16 to 205 Ma, y = (–0.006 ± 0.001)x + (2.64 ± 0.12), R = 0.38; (iii) $\Delta\delta^{13}C_{org}$ = 3.2‰ for 0 to 40 Ma, y = (–0.08 ± 0.01)x + (–22.1 ± 0.02), R = 0.78; (iv) $\Delta\delta^{13}C_{org}$ = 0.8‰ for 40 to 205 Ma, y = (–0.005 ± 0.003)x + (–24.8 ± 0.38), R = 0.17. We note that including the Lower Jurassic section (Mochras borehole data) in the linear regression produces a lower rate of increase in $\delta^{13}C$, which yields a more conservative estimate of the magnitude of the long-term increase. We used a singular spectrum analysis to highlight the long-term $\delta^{13}C$ variations; $\delta^{13}C$ data were linearly interpolated (100,000-year sampling interval) and analyzed using the SSA-MTM Toolkit from www.atmos.ucla.edu/tcd/ssa (*30*). Singular spectrum analysis (SSA) was performed using a 205-point (~20 My) window with the Broomhead and King method for constructing the covariance matrix; the six highest variance components were added together to reconstruct the long-term $\delta^{13}C$ variations.

on land (*6*), appears to have had a profound influence on the evolutionary trajectories of metazoans.

Whereas the relatively rapid decline in oxygen at the end-Permian and early Triassic is suggested to have been a major factor contributing to the extinction of terrestrial animals (mostly reptiles) at this time (*15*), the rise of oxygen over the ensuing 150 My almost certainly contributed to evolution of large animals. Animals with relatively high oxygen demands, including theropod dinosaurs (the group that includes living birds) and small mammals (*19*, *20*), evolved by the Late Triassic. Avian and mammalian metabolic demands are three to six times as high per unit biomass as those of reptiles (*21*). Although the reproductive strategies of the earliest mammals are not known with certainty, both the fossil record and molecular divergence indicate that superordinal diversification of placental mammals occurred between 65 and 100 Ma (*20*, *22*, *23*). This radiation corresponds to a period of relatively high and stable oxygen levels in the atmosphere (Fig. 2). Although placental evolution is not unique to mammals (*24*), this reproductive strategy, which can facilitate geographic expansion of a species, requires relatively high ambient oxygen concentrations (*25*, *26*). In the placenta, maternal arterial blood, with oxygen levels near ambient alveolar pressure, mixes with placental venous blood in a sinuslike vascular structure. Fetal umbilical arterial (really venous) blood arrives in a capillary network in the maternal sinus where oxygen diffuses into the fetal blood. The nature of this exchanger requires the mammalian fetus to live at a very low arterial oxygen pressure. Al-

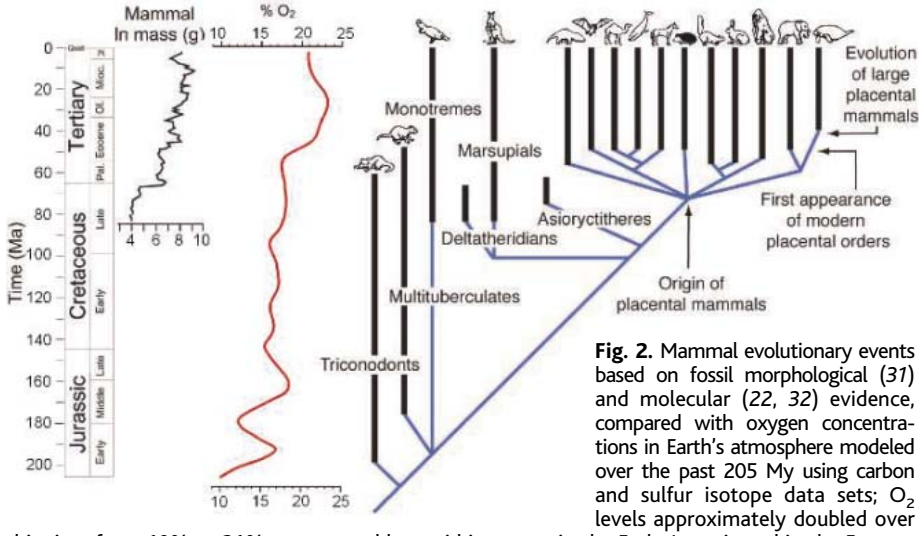

Fig. 2. Mammal evolutionary events based on fossil morphological (*31*) and molecular (*22*, *32*) evidence, compared with oxygen concentrations in Earth's atmosphere modeled over the past 205 My using carbon and sulfur isotope data sets; O_2 levels approximately doubled over this time from 10% to 21%, punctuated by rapid increases in the Early Jurassic and in the Eocene. Changes in average mammalian body mass is taken from (*27*). Vertical black bars represent known fossil ranges, blue lines represent inferred phylogenetic branching. Only some of the ordinal-level placental mammals are shown.

though at low oxygen, placental hemoglobin binding affinity for O_2 is modified by pH (i.e., the Bohr effect), with exceptions, few extant mammals reproduce above elevations of ~4500 m, corresponding to atmospheric oxygen levels in the Early Jurassic (*15*).

Whereas a bolide impact at the Cretaceous-Tertiary (K-T) boundary and the ensuing extinction of dinosaurs provided ecological opportunity for the radiation of placental mammals, the rise of oxygen in the Eocene corresponds to a large increase in average mammalian body size (*27*). The density of capillaries per unit muscle scales to the 0.87 power of size in mammals (*28*); hence, larger animals require high ambient O_2 levels to obtain maximal metabolic rates. Comprehensive study of body mass of nearly 2000 fossil mammals in the North American record indicates a steady expansion in size range throughout the Cenozoic, tracked by mean body size due to the static lower limit of size (*27*). Data show a rapid increase from small to medium-sized mammals in the first few million years after the K-T event (Fig. 2). This size contrast is blurred slightly with the recent discovery of larger Cretaceous mammals (*29*), but this trend does not appear to be driven by oxygen. A second upward surge in mean body mass is recorded for the early through middle Eocene (50 to 40 Ma) (*27*), followed by further but less dramatic size increases through the Miocene. This trend tracks a change in oxygen. The early to middle Eocene, an interval characterized by the highest global mean annual temperatures and the broadest latitudinal span of warm subtropical to temperate faunas and floras for the Cenozoic, was also a time of high morphological disparity in North American placental mammals. One might infer that this indicates a proliferation of ecological roles in the North American mammalian fauna. Notably, many of the living placental orders appear in the early Eocene, and artiodactyls, the dominant large terrestrial herbivores today, underwent a massive radiation in the mid-Eocene (*27*). Data from other continents are more limited, but there is reason to argue that North America serves as a model for broader patterns, at least in the northern hemisphere. The substantially improving records in Europe and Asia, especially, will provide an interesting test of the pattern.

The data presented here provide evidence of a secular increase in atmospheric oxygen over the past 205 My that broadly corresponds with three main aspects of vertebrate evolution, namely endothermy, placentation, and size. Particularly notable are high stable O_2 levels during the time of placental mammal origins and diversification and a close correspondence between marked increases in both atmospheric oxygen levels and mammalian body size during the early to middle Eocene. Although increases in mammalian body size, morphological disparity, and inferred ecological heterogeneity during this interval may have been influenced as well by other environmental factors such as warm global temperatures and the spread of tropical and subtropical habitats, the correlation between evolutionary changes in mammalian body size and increased atmospheric O_2 has a physiological basis related to placental mammal reproduction. The changes in oxygen appear to have been driven by tectonics and increased burial efficiency of organic matter on continental margins.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/309/5744/2202/DC1
Materials and Methods
Tables S1 and S2
References

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Preindustrial to Modern Interdecadal Variability in Coral Reef pH

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The oceans are becoming more acidic due to absorption of anthropogenic carbon dioxide from the atmosphere. The impact of ocean acidification on marine ecosystems is unclear, but it will likely depend on species adaptability and the rate of change of seawater pH relative to its natural variability. To constrain the natural variability in reef-water pH, we measured boron isotopic compositions in a ~300-year-old massive *Porites* coral from the southwestern Pacific. Large variations in pH are found over ~50-year cycles that covary with the Interdecadal Pacific Oscillation of ocean-atmosphere anomalies, suggesting that natural pH cycles can modulate the impact of ocean acidification on coral reef ecosystems.

Since the beginning of the industrial revolution, the burning of fossil fuels has increased the CO_2 content of the atmosphere from ~280 to more than 370 parts per million per volume (ppmv), a level unprecedented in the last 420,000 years (*1*). To date, a large part of anthropogenic CO_2 emissions has been absorbed by the oceans (*2*), which have become more acidic, thus reducing their capacity to continue to absorb CO_2. Estimates of global oceanic pH trends to the year 2000 indicate that the oceans have already acidified by 0.1 pH units relative to preindustrial times (*3*, *4*). Geochemical models forecast an exponential decrease of nearly 0.8 pH units by 2300 (*4*), a scenario for which there is no obvious

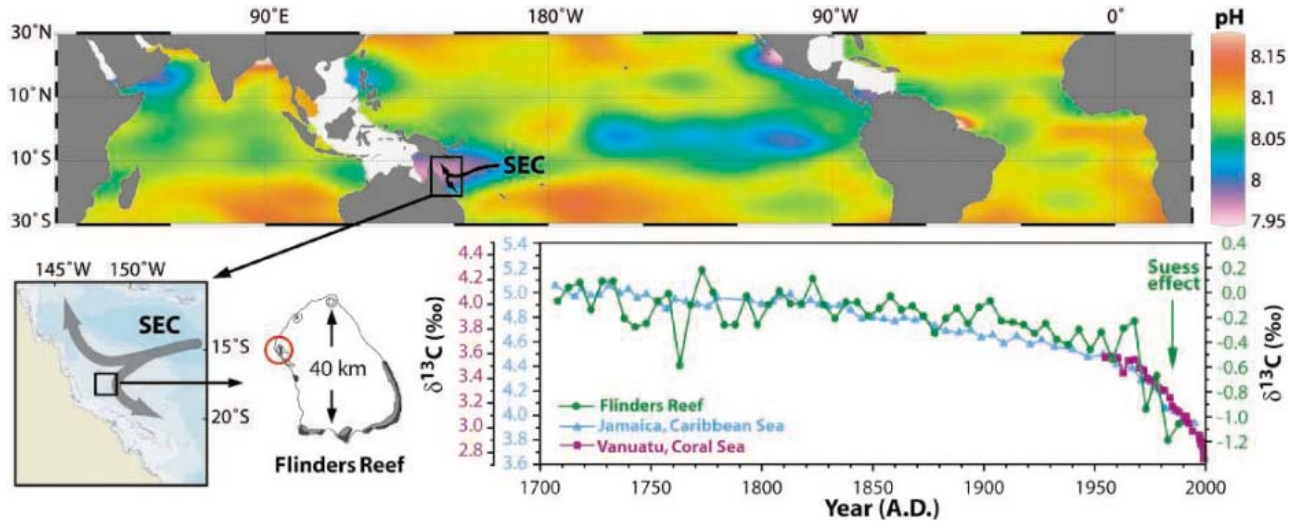

Fig. 1. Distribution of present-day surface-ocean pH, location of the Flinders Reef coral site, and record of coral $\delta^{13}C$ since 1708 A.D. **(Top)** Map showing present-day mean annual surface pH (*24*). **(Left)** Locality map showing Flinders Reef and approximate path of the SEC and sketch showing the location and dimensions of Flinders Reef. Coral core FL02A was drilled on the North West Reef (17.5°S, 148.3°E; red circle). **(Right)** The $\delta^{13}C$ data for the Flinders Reef coral and coralline sponges, *Ceratoporella nicholsoni* (Jamaica) (*25*) and *Acanthochaetes wellsi* (Vanuatu) (*26*), show a progressive depletion of ^{13}C in surface seawater, which can be ascribed to the Suess effect.

precedent over the last hundreds of millions of years (*5*), with the possible exception of abrupt changes such as those associated with the Paleocene/Eocene Thermal Maximum 55.5 million years ago (*6*). Experimental evidence indicates that such reductions in surface-ocean pH and carbonate saturation state could have major effects on calcifying marine biota (*7*), especially calcareous plankton (*8*) and coral reef communities, where the degree of carbonate supersaturation has been shown to have a major effect on calcification rates (*9*–*11*).

The actual trend and range of natural variability in oceanic pH remains largely unknown, yet it is crucial to understand the possible consequences of acidification on marine ecosystems. A reliable proxy record is needed to assess long-term trends and variability in seawater pH. Instrumental records of the seawater CO_2 system, such as those collected at the Hawaii Ocean Time Series Station, which only commenced in 1989 (*12*), are short. In this Report, we present a reconstruction of seawater pH spanning the last three centuries, based on the boron isotopic composition ($\delta^{11}B$) (*13*) of a long-lived massive coral (*Porites*) from Flinders Reef in the western Coral Sea (Fig. 1).

The potential of $\delta^{11}B$ in biogenic carbonates as a proxy for paleo-pH was first realized during the early 1990s (*14*, *15*), and reconstructions of seawater pH using foraminifera have since been reported (*16*–*19*). Although the feasibility of using $\delta^{11}B$ in corals to track changes in pH has been appreciated (*14*, *15*, *20*, *21*), no long-term continuous records of coral $\delta^{11}B$-derived pH have been reported. Culture experiments on *Porites* and *Acropora* have confirmed that corals faithfully record variations in seawater pH (*22*, *23*), but there is still some uncertainty about how "vital" effects associated with coral calcification may influence pH proxy records (*22*). The calibration of $\delta^{11}B$ ratios with seawater pH for *Porites* grown under controlled conditions is in good agreement with the theoretical curve for the borate species (*22*), the major form in which boron is incorporated into coral skeletons (*14*, *15*). In this study, we determined a record of seawater pH from $\delta^{11}B$ ratios for a *Porites* coral (*24*) from Flinders Reef in the Coral Sea (Fig. 2A and fig. S1). The full length of the coral core was sampled in 5-year increments, providing a continuous record of seawater pH that commences in 1708 A.D., well before the start of the Industrial Revolution. This record provides a natural baseline against which the long-term effects of ocean acidification on reef-water pH can be assessed.

Figure 1 shows the coral $\delta^{13}C$ record for the period 1708 to 1988 A.D., derived from the same 5-year sample increments as those analyzed for $\delta^{11}B$ (*24*). The most notable feature of the $\delta^{13}C$ curve is the trend toward lower values commencing from 1800 A.D. Similar trends have been recorded in scleroSponges from Jamaica in the Caribbean Sea and from Vanuatu in the Coral Sea (*25*, *26*) (Fig. 1). The secular decrease in coral $\delta^{13}C$ can be ascribed to the Suess effect, which is due to uptake by the oceans of atmospheric CO_2 that has been progressively depleted in ^{13}C by combustion of fossil fuels.

Although the lowest $\delta^{11}B$ value for the entire record corresponds to the 5-year average around 1988 [23.0 per mil (‰), 7.91 pH units; Fig. 2A and table S1], there is no notable trend toward lower $\delta^{11}B$ values. The dominant feature of the coral $\delta^{11}B$ record is a clear interdecadal oscillation of pH, with $\delta^{11}B$ values ranging between 23 and 25‰ (7.9 and 8.2 pH units; Fig. 2A). Spectral analysis of the coral pH record demonstrates a substantial cyclicity of about 50 years (Fig. 2A and fig. S2). Moreover, the variation in pH is synchronous with the Interdecadal Pacific Oscillation (IPO) (*27*), the Pacific-wide equivalent of the Pacific Decadal Oscillation (PDO) (*28*), which is also well represented by a 50- to 70-year cyclicity (*29*) (Fig. 2B and fig. S2). The IPO is well represented by a spatial pattern of sea surface temperature (SST) anomalies over the Pacific Ocean, such that the index is positive when the equatorial Pacific is warm and the southwest Pacific and central North Pacific are cold. This pattern of interdecadal climate variability shares similarities with the El Niño-Southern Oscillation (ENSO), with periods of positive and negative IPO values displaying climatic patterns similar to El Niño and La Niña, respectively (*30*, *31*).

The covariation of the Flinders paleo-pH record and the IPO provides insight into possible mechanisms driving long-term interdecadal variation in seawater pH at the study site. One mechanism for lowering pH could be vertical mixing and upwelling of subsurface (hence more acidic) waters during periods

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of positive IPO. However, upwelling would produce SSTs substantially cooler than average, which is inconsistent with the coral Sr/Ca record given that there is no correlation between Sr/Ca and pH (*32*). Also, upwelled low pH water would bring cooler and saltier Subtropical Lower Waters to the surface, as observed during upwelling intrusions into the Great Barrier Reef (*33*). However, paleosalinity estimates from coupled analysis of coral $\delta^{18}O$ and Sr/Ca in the Flinders Reef coral (*24*) indicate that there is no correlation between low pH and high salinity (*32*).

Given the present-day differences observed in surface-ocean pH throughout the tropical Pacific (~0.2 units; Fig. 1), interdecadal changes in surface currents and the redistribution of water masses could be another factor affecting surface-ocean pH. The stronger and/or more frequent La Niña events that develop during times of negative IPO (*30*) would enhance the strength of the South Equatorial Current (SEC) (*34*) and bring higher pH surface waters into the Flinders Reef area, in agreement with the coral $\delta^{11}B$ record (Fig. 2). However, this could not account for the full range of pH variability (~0.3 units) inferred from the Flinders Reef coral.

The most likely explanation for the variability in pH at Flinders Reef is that coral reef calcification combined with limited flushing of reef water exerts an important local control over the extent of the buildup of partial pressure of CO_2 (PCO_2) within the reef. This is consistent with observations at other reefs, such as those in the Indo-Pacific region (*35*), where the residence time of lagoon water influences the carbon budget of reef water. Flinders Reef is also likely to be influenced by these processes because it is one of the largest discrete reef systems in the Coral Sea, about 40 km north to south, with a continuous barrier of about 15 km along the eastern side (Fig. 1). The platform reef is directly flushed by the SEC (Fig. 1), whose strength is proportional to Pacific trade-wind velocity, which ultimately controls the exchange of Flinders Reef water with the open ocean. During periods of positive IPO (similar to El Niño) when the Pacific tradewinds and SEC are relatively weak (*34*), renewal of the Flinders Reef water would also be slower and the consequent buildup of CO_2 through calcification would lower the ambient seawater pH. This is the same phase in which the IPO and Flinders Reef pH are correlated, with positive IPO corresponding to low pH and negative IPO corresponding to high pH (Fig. 2). Moreover, changes in western Pacific sea level with the ENSO phase [up to ~30 cm in areas of the South Equatorial Pacific (*34*)] would also affect the rate of exchange of lagoonal water at Flinders Reef. During positive IPO phases (similar to El Niño), lower sea levels would further reduce the renewal of reef waters, thus enhancing the buildup of CO_2 and lowering pH. In contrast, more efficient flushing of reef water during the negative IPO phase (similar to La Niña) would explain the higher pH values (Fig. 2).

High-resolution analysis of $\delta^{11}B$ in the Flinders Reef coral provides a seasonal record of reef-water pH that lends support to this mechanism (Fig. 2C). The seasonal pH record, spanning April 1987 to April 1988, shows a tendency to covary with wind speed recorded nearby at Willis Island (16.3°S, 150.0°E), where strong winds occur at times of high seawater pH and weak winds occur at times of low seawater pH at Flinders Reef (Fig. 2). The seasonal rise in reef-water pH (March/April) also coincides with the seasonal intensification of the SEC (*36*). Conversely, pH displays minimum values from October to March, when the SEC is weaker (*36*), allowing for a buildup of reef-water CO_2. This mechanism explains the lower seawater pH values for Flinders Reef relative to open ocean waters; it is only at times of efficient lagoonal flushing (e.g., ~1960 A.D.) that reef-water pH reaches values typical of the open ocean (pH = ~8.1 to 8.2).

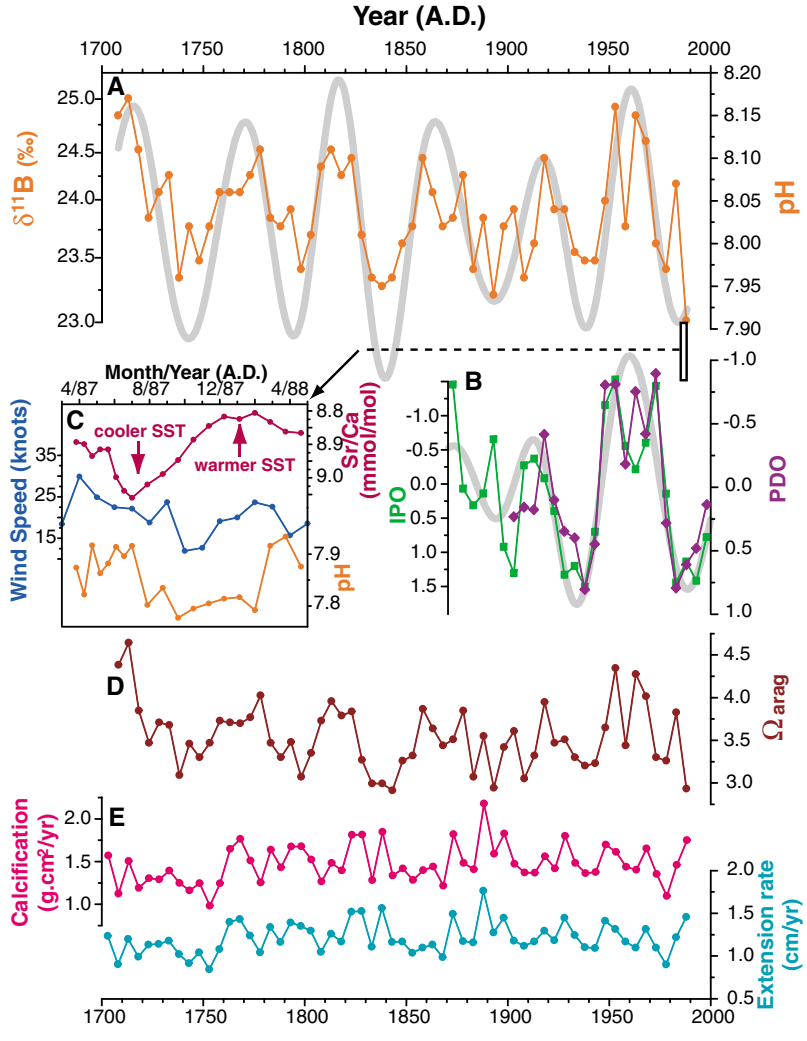

Fig. 2. Record of Flinders Reef coral $\delta^{11}B$, reconstructed oceanic pH, aragonite saturation state, PDO and IPO indices, and coral calcification parameters. (**A**) Flinders Reef coral $\delta^{11}B$ as a proxy for surface-ocean pH (*24*); $\delta^{11}B$ measurements for all 5-year intervals are available in table S1. (**B**) Indices of the PDO (*28*, *39*) and the IPO (*27*) averaged over the same 5-year intervals as the coral pH data. Gray curves in panels (A) and (B) are the outputs of Gaussian filtering of coral pH and IPO values, respectively, at a frequency of 0.02 ± 0.01 year^{-1}, which represent the 1/50-year component of the pH variation (fig. S2). (**C**) Comparison of high-resolution coral Sr/Ca (plotted to identify the seasonal cycle of SST) (*32*), $\delta^{11}B$-derived pH, and wind speed recorded at the Willis Island meteorological station (data from the Australian Bureau of Meteorology) (*40*). Note the covariation of wind speed and seawater pH; strong winds generally occur at times of high pH, and weak winds generally occur at times of low pH. All high-resolution $\delta^{11}B$ measurements are available in table S2. (**D**) Aragonite saturation state, $\Omega_{arag} = [Ca^{2+}][CO_3^{-2}]/K'_{sp}$, where K'_{sp} is the stoichiometric solubility product of aragonite, calculated from our reconstructed pH assuming constant alkalinity (*24*). (**E**) Coral extension and calcification rates obtained from coral density measured by gamma ray densitometry (*38*).

Regardless of the mechanism controlling reef-water pH, our results suggest that corals at Flinders Reef have experienced a relatively wide range in pH (~0.3 pH units) over the past ~300 years. As a result, these corals have also experienced equivalent changes in the aragonite saturation state (Ω_{arag}), one of the main physicochemical controllers of coral calcification. Changes in Ω_{arag} have been derived from the Flinders pH record (Fig. 2D), with Ω_{arag} varying from ~3 to 4.5, assuming constant alkalinity (*10*, *24*). This encompasses the lower and upper limits of Ω_{arag} within which corals can survive (*37*). Despite such marked changes, skeletal extension and calcification rates for the Flinders Reef coral (Fig. 2E) fall within the normal range for *Porites* (*38*) and are not correlated with Ω_{arag} or pH. Therefore, the *Porites* coral at Flinders Reef seems well adapted to relatively large fluctuations in seawater pH and Ω_{arag}.

The interdecadal cycle in seawater pH observed at Flinders Reef has relevance for predicting its response to future ocean acidification, given that it will either enhance or moderate the local effects of the projected long-term decrease in pH (*3*, *4*). For example, the next rise in the ~50-year cycle of reef-water pH should counteract the lowering of pH values at Flinders Reef until ~2035 A.D. Conversely, the subsequent fall in the reef-water pH cycle will lead to an abrupt shift toward low pH reef water. The extent to which corals and other calcifying reef organisms can adapt to such rapid decreases in pH is largely unknown.

Our findings suggest that the effects of progressive acidification of the oceans are likely to differ between coral reefs because reef-water P_{CO_2} and consequent changes in seawater pH will rarely be in equilibrium with the atmosphere. Although the relatively large variations in seawater pH at Flinders Reef suggest that coral reefs may be resilient to the shorter term effects of ocean acidification, in the coming decades many reefs are likely to experience reduced pH that is unprecedented relative to "natural" levels. Additional paleo-pH records are required from a range of coral reef ecosystems to improve our understanding of the physical and biological controls on reef-water pH, and the long-term impacts of future ocean acidification.

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Materials and Methods
Figs. S1 and S2
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Phylogenetic MCMC Algorithms Are Misleading on Mixtures of Trees

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Markov chain Monte Carlo (MCMC) algorithms play a critical role in the Bayesian approach to phylogenetic inference. We present a theoretical analysis of the rate of convergence of many of the widely used Markov chains. For *N* characters generated from a uniform mixture of two trees, we prove that the Markov chains take an exponentially long (in *N*) number of iterations to converge to the posterior distribution. Nevertheless, the likelihood plots for sample runs of the Markov chains deceivingly suggest that the chains converge rapidly to a unique tree. Our results rely on novel mathematical understanding of the log-likelihood function on the space of phylogenetic trees. The practical implications of our work are that Bayesian MCMC methods can be misleading when the data are generated from a mixture of trees. Thus, in cases of data containing potentially conflicting phylogenetic signals, phylogenetic reconstruction should be performed separately on each signal.

Bayesian inference is one of the most popular methods in phylogeny reconstruction (*1*). Many widely used software packages, such as MrBayes (*2*), BAMBE (*3*), and PAML (*4*), rely on Markov chain Monte Carlo (MCMC) methods. These algorithms are often known as BMCMC. Part of the appeal of BMCMC is that they are supposed to be more robust and faster than standard maximum likelihood approaches. Our results show that these appealing features are overly optimistic in some settings.

The basis of the MCMC algorithms is a Markov chain whose stationary distribution is the desired posterior distribution. Reliable phylogenetic estimates depend on the Markov chain converging to the posterior distribution

before any phylogenetic inferences are made. Typically it is elementary to establish that the Markov chains eventually converge to the posterior distribution. However, convergence after an infinite number of iterations is not of practical use. The chains need to converge quickly to the posterior distribution in order to be considered useful. Unfortunately, it is notoriously difficult to rigorously analyze the convergence rate of the Markov chains used for phylogeny. In practice, heuristics [such as multiple starting states and convergence of log-likelihood plots (*5*)] are commonly used to determine when the Markov chains have converged to the posterior distribution.

The major difficulty in analyzing these Markov chains is our poor understanding of the geometry of the space of tree topologies weighted by the likelihood function (this geometric space is often referred to as the tree space). Work has been done on the likelihood function for fixed trees on three and four leaves (*6*, *7*) [abstract properties of tree space on any number of leaves also have been analyzed (*8*–*11*)].

In our work, we consider N characters generated from a uniform mixture of two trees on $n \geq 5$ leaves and show that BMCMC takes an exponential number of iterations to converge. Our proofs also yield detailed information on the geometry of the likelihood function on the tree space for five or more leaves. It has its basis in combinatorial analysis techniques that are further discussed in (*12*).

The bases of our results are the following two trees of five taxa: T_1 is given by ((12),3),(45) in the standard Newick format, whereas T_2 is given by ((14),3),(25); see the yellow trees in Fig. 1 for an illustration. Our results apply to cases where the data are generated from a uniform mixture of two trees, $(T_1^*,\vec{L}_1^*)$ and $(T_2^*,\vec{L}_2^*)$, on $n \geq 5$ leaves, where for some subset S of leaves, the subtree of $(T_1^*,\vec{L}_1^*)$ on S is $(T_1,\vec{l}_1)$, and the subtree of $(T_2^*,\vec{L}_2^*)$ on S is $(T_2,\vec{l}_2)$. Moreover, the branch lengths on subtrees $(T_1,\vec{l}_1)$ and $(T_2,\vec{L}_2^*)$ must lie in the following zone: The branch lengths of terminal branches (i.e., edges incident to the leaves) are between a and a^2; the branch lengths of internal branches are between a and $2a$; and the number a satisfies $0 < a < b$, where b is some small positive constant. The assumptions on the branch lengths of T_1 and T_2 are essential in the details of the proof.

For each of the trees $(T_1^*,\vec{L}_1^*)$ and $(T_2^*,\vec{L}_2^*)$, the character data are generated by using any of the standard mutation models, such as the Cavender-Farris-Neyman (CFN) model, the Jukes-Cantor model, and Kimura's two parameter model [see (*13*) for an introduction to these models]. Moreover, our results hold for almost any prior distribution on branch lengths used in BMCMC including those discussed in (*14*, *15*); see (*12*) for more details.

Our results are valid for two families of BMCMC. In the first family, the MCMC performs a random walk on the discrete set of tree topologies. The transition probabilities are determined by the Metropolis rule (*16*) using the Bayesian probability of tree topology given the data (*14*). In the second family, we consider MCMC performing a random walk on the continuous space of tree topologies and branch lengths (*3*, *17*). For both families the moves that change the tree topology may be nearest-neighbor interchanges (NNI), subtree pruning and regrafting (SPR), or tree bisection and reconnection (TBR) moves; see (*14*) for an introduction to these transitions.

In order to measure convergence of the Markov chain, we use the notion of mixing time, T_{mix}, which is standard in probability theory (*18*). The mixing time is, for the worst initial state T_0, the first time that the total variation distance between the distribution of T_t (i.e., the chain at time t) and the stationary distribution is at most 1/4. (The constant 1/4 is somewhat arbitrary and simply needs to be <1/2.) The above definition of mixing time implies that for any $\varepsilon > 0$, after $\leq T_{\text{mix}}$ iterations, the Markov chain is variation distance $\leq \varepsilon$ from the stationary distribution.

We can now state our main theoretical result: There exists a constant $c > 0$ such that in the setting described above, given N characters, $\vec{D} = (D_1,\ldots,D_N)$, generated from the mixtures of $(T_1^*,\vec{L}_1^*)$ and $(T_2^*,\vec{L}_2^*)$ on $n \geq 5$ taxa, with probability at least $1 - \exp(-cN)$ over the data generated, the mixing time of MCMC algorithms with NNI, SPR, or TBR transitions is at least $\exp(cN)$.

The formal proof of this statement appears in (*12*). We follow with a heuristic argument. The algorithmic computations below were performed for both the binary CFN model (*19*–*21*) and the Jukes-Cantor model. In both of these models, the branch length $a = \alpha t$ where α is the rate from state i to j, for $i \neq j$, and t is time.

The convergence properties of a Markov chain requires a detailed understanding of the weighted geometry of the state space. One aspect of the geometry is depicted in Fig. 1. In this figure, two trees are joined by an edge if they are connected by a single NNI transition. One can see that our two generating trees T_1 and T_2 have maximum distance.

The second aspect of the geometry are the posterior probabilities of tree topologies. The posterior probability of tree topology T is denoted by $w(T)$. It is natural to expect that for long sequences, $w(T)$ is essentially determined by the branch lengths that maximize the expected log-likelihood. In other words,

$$\frac{\log w(T)}{N} \sim J(T) = \max_{\vec{l}} E[\log \Pr(D|T,\vec{l})]$$

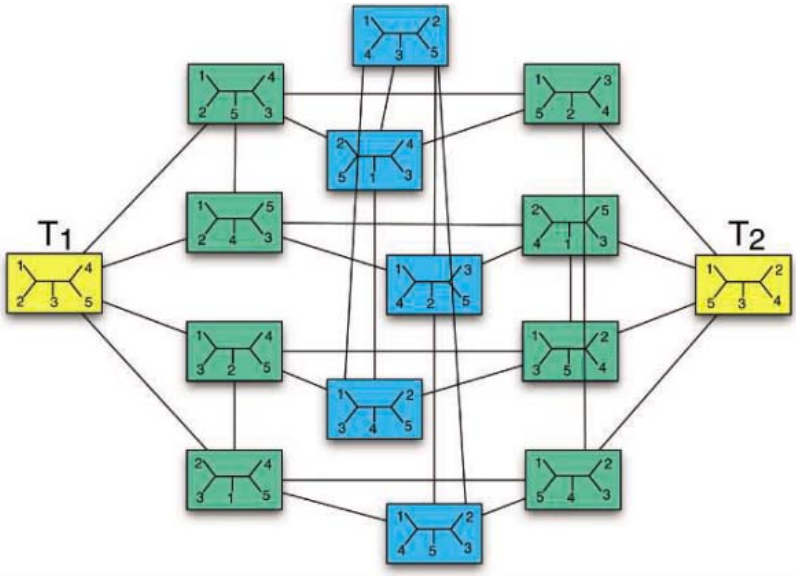

Fig. 1. The space of phylogenetic trees on five taxa connected by NNI transitions. For the mixture distribution on T_1 and T_2 in the CFN model with internal branch lengths $a = 0.1$ and terminal branch lengths $a^2 = 0.01$, the yellow trees, with optimal branch lengths, had expected log likelihood $J(T) \approx -1.887$, the green trees had $J(T) \approx -1.934$, and the blue trees had $J(T) \approx -1.986$. For the Jukes-Cantor model with $a = 0.1$, the yellow trees had $J(T) \approx -4.293$, the green trees had $J(T) \approx -4.338$, and the blue trees had $J(T) \approx -4.544$. Note, for SPR and TBR transitions, each yellow tree is connected to 12 other trees but not to each other. Thus, to travel between the two yellow trees by NNI, SPR, or TBR transitions, we need to traverse through a valley (i.e., trees with lower log-likelihood).

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where the expectation is over the probability distribution μ generating the data.

Figure 1 considers the expected log-likelihood $J(T)$ for data generated by taking independent samples from our mixture μ of the two trees T_1 and T_2 on five taxa, where all internal branches have length $a = 0.1$ and all terminal branches have length $a^2 = 0.01$. In Fig. 1, our generating trees have maximum expected log-likelihood $J(T)$, and the intermediate trees in this space have smaller expected log-likelihood. Thus, to traverse between the two maxima trees, we need to traverse a valley. Such a valley implies slow convergence, via mathematical techniques known as conductance and isoperimetric inequalities (*18*).

A similar picture holds for SPR and TBR transitions. On trees on five taxa TBR and SPR moves are identical. To traverse between the trees with maximum expected likelihood, T_1 and T_2, we need to pass through trees with smaller expected likelihood. This is the key property that implies slow convergence. For SPR and TBR transitions, tree T_1 and T_2 are connected to 12 other trees but not to each other.

In Fig. 2 we show how the maximum expected log-likelihood $J(T)$ varies with the NNI distance from the generating trees T_1 and T_2 for varying values of internal branch length a in the generating trees, where the terminal branch lengths are given by a^2.

The implications of mixture distributions to phylogeny has recently received considerable theoretical attention (*22*, *23*) and has clear practical importance. A simple example that often contains characters from multiple trees is molecular data consisting of DNA sequences for more than one gene. It is well known that phylogenetic trees can vary between genes [for example, see (*24*) for a discussion].

The numerical values of the constants a and c are not explicit in our results. However, simulations suggest that even moderate values such as $a = 0.1$ and $N = 1000$ have very slow convergence, and in fact starting at the tree T_1 or T_2 it will never visit any other tree topology. Moreover, in both cases, the likelihood plot suggests quick convergence. For these parameters, the behavior of the chain on data coming from mixtures or from data generated from a single tree is indistinguishable for as long as we run our experiments (millions of iterations). See fig. S1 (*12*) for log-likelihood plots illustrating these examples.

For small trees one can hope to overcome the slow convergence by using multiple starting states. However, mixtures coming from large trees may contain multiple species subsets where one tree has T_1 as an induced subtree and the other has T_2. If there are k such subsets, then about 15^k random starting points will be needed. Thus if there are 10 disagreement subsets, then 15^{10} random starting points will be needed in order to sample from the posterior distribution.

A popular MCMC program for phylogeny, MrBayes (*2*), uses Metropolis-coupled MCMC (*25*), which is designed to avoid bottlenecks in the state space. A key open question is to understand whether Metropolis-coupled MCMC is successful in avoiding bottlenecks created by mixtures. Resolving this question will require more delicate and detailed mathematical analysis. It is known that Metropolis-coupled MCMC converges exponentially slowly in some settings but avoid bottlenecks in others (*26*), but even in these simple cases a very detailed understanding of the state space is needed. If Metropolis-coupled MCMC successfully avoids the bottlenecks created by mixtures, then it may serve as a useful tool for identifying data generated from mixtures.

In our setting, BMCMC methods fail in a clearly demonstrable manner. We expect that there is a more general class of mixtures where BMCMC methods fail in more subtle ways. These subtle failures may occur for many real-world examples where the Markov chains quickly converge to some distribution other than the desired posterior distribution. Users of BMCMC methods should ideally avoid mixture distributions that are known to produce degenerate behavior in various phylogenetic settings (*27*, *28*). A good practice is to decompose the data into nonconflicting signals and perform phylogenetic reconstruction separately on each signal. Our work highlights important unresolved questions: how to verify homogeneity of genomic data and what phylogenetic methods can efficiently deal with mixtures.

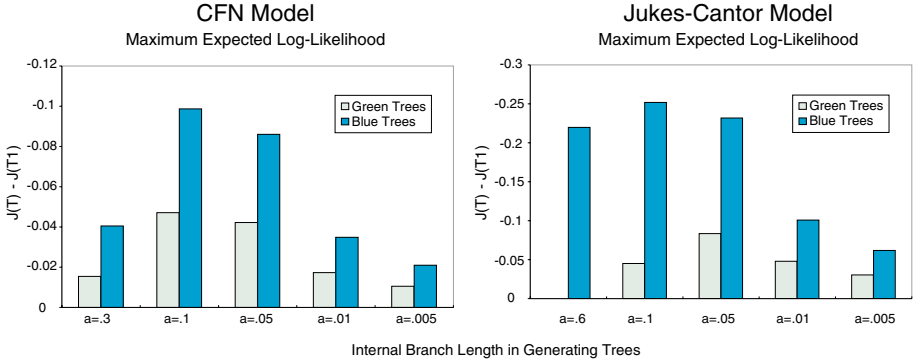

Fig. 2. The depth of the valley between the generating trees T_1 and T_2 with five taxa. The chart shows the maximum expected log-likelihood for different classes of trees for varying generating parameter a where the internal edges have length a and the terminal edges have length a^2. For the green trees and blue trees from Fig. 1, we plot the value of $J(T) - J(T_1)$. For the yellow trees (i.e., the generating trees T_1 and T_2), this value is 0.

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Dynamic Paternity Allocation as a Function of Male Plumage Color in Barn Swallows

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Paternity in male animals can be influenced by their phenotypic signals of quality. Accordingly, the behavior underlying patterns of paternity should be flexible as signals of quality change. To evaluate the dynamics of paternity allocation, we analyzed paternity before and after manipulating plumage coloration, a known signal of quality, in male barn swallows *Hirundo rustica*. We found that, in successive breeding bouts, only males whose plumage color was experimentally enhanced received greater paternity from their social mates, demonstrating evidence for flexible and dynamic paternity allocation and the importance for males of maintaining signals of quality well after pair bond formation.

Extrapair fertilizations are common in organisms with socially monogamous breeding systems (*1*, *2*). It is widely viewed that extrapair mating is an adaptive, flexible response to variability in the quality of potential mates within and among breeding attempts (*2*–*6*). However, despite dozens of studies on extrapair mating, we know remarkably little about the dynamics of paternity allocation. Many studies have shown differential allocation of paternity in relation to features of mate quality (*1*), but the strongest evidence for an association between male quality and paternity allocation would come from studies in which paternity was assessed both before and after male signals of quality are manipulated experimentally. However, to date, male ornament manipulations have been conducted only before (*7*, *8*) or just after (*9*–*11*) the male has formed a social pair bond and, in every case, before a first breeding attempt.

Comparing a male's paternity in successive breeding attempts, before and after his phenotype is manipulated, is critical for rigorously studying the dynamics of paternity allocation, because it allows one to (i) assess the dynamics of paternity allocation within the same breeding pair; (ii) control for potentially confounding variables such as female quality, familiarity between social mates, and interactions between female and male quality, all of which could strongly influence paternity allocation (*1*); and thereby (iii) analyze directly the relationship between successive paternity outcomes and whether they are affected by phenotypic signals of male quality.

We studied the dynamics of paternity allocation as a function of an experimentally manipulated signal of mate quality in barn swallows (*Hirundo rustica erythrogaster*) from North America. Extrapair fertilizations are common in this socially monogamous species (*7*, *12*). Unlike in European populations of barn swallows (*H. r. rustica*), where elongate tail streamers function as sexual signals (*7*), ventral plumage coloration is a sexually selected trait in our study population of *H. r. erythrogaster* (*13*).

We used a paired design to test whether within-season changes in male coloration affect paternity allocation in two successive breeding attempts. Before the start of the experiment, we captured each adult and collected morphological data and a blood and feather sample (*14*). To determine whether individuals (females or conspecific males) assess male quality dynamically during the breeding season, we (i) allowed a female to settle with a mate and lay a complete clutch of eggs and (ii) recaptured and randomly assigned males to one of three treatment groups: their feather coloration was enhanced within the natural range of variation (fig. S1), or they were placed in one of two control groups, a sham manipulated group or an unmanipulated group (*15*). We simultaneously (iii) removed the first clutch to simulate a nest failure, thereby inducing the female to lay a replacement clutch after she had the opportunity to reassess her social mate's quality.

DNA samples from each embryo in the first clutch and from each nestling in the replacement brood were used to compare paternity allocation to the same male as a function of changes in signals of male quality by directly analyzing differences in the proportion and number of extrapair young between the first and the replacement clutches of males in each treatment group. We used microsatellite-based analyses to determine the paternity of offspring in first versus replacement broods in order to directly examine changes in a male's paternity in response to the experimental manipulation (*15*).

In the clutches laid before plumage color was manipulated, there were no initial differences in paternity across treatments [number of young sired by focal male/total number of young in clutch, logistic model, $\chi^2 = 0.09$, $P > 0.95$; number of a male's own young in nest, analysis of variance (ANOVA) $F_{2, 27} = 0.07$, $P > 0.90$] (Fig. 1). In the subsequent breeding attempt, however, there was a significant effect of our plumage manipulation on paternity (differences in proportion of paternity, ANOVA $F_{2, 24} = 4.0$,

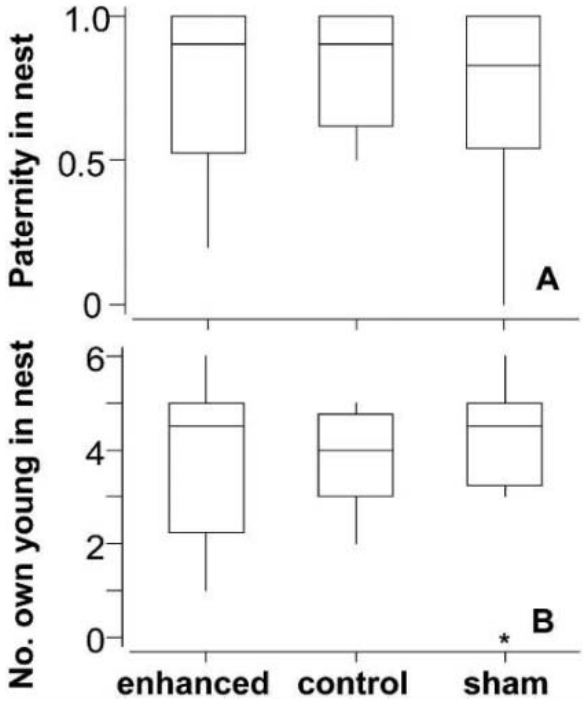

Fig. 1. (**A**) The proportion of within-pair young sired by males in three treatment groups did not differ at the start of the experiment. (**B**) The number of offspring in the nest that were sired by the focal male did not differ across treatments at the start of the experiment. These box and whisker plots portray the median value (line across box), and the first and third quartiles (boxes below and above median line, respectively). Whiskers indicate lines that extend from the bottom and top of the box to the lowest and highest values adjacent to the box that are defined by the following limits: lower limit = [quartile 1 − 1.5(quartile 3 − quartile 1)] and upper limit = [quartile 3 + 1.5(quartile 3 − quartile 1)]. The asterisk in (**B**) indicates an outlier outside of the lower limit.

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$P < 0.04$; differences in number of a male's own young in nest, ANOVA $F_{2, 23} = 5.45$, $P < 0.02$) (Fig. 2). Posthoc pairwise comparisons (Tukey's test at $P < 0.05$) indicate that the paternity and number of young of males in the enhanced treatment were significantly greater than the paternity or number of young of males in both control groups and that both control groups did not differ from one another for either measure of paternity. That males with enhanced plumage color gained paternity in replacement clutches, whereas males in both control groups did not, provides compelling evidence for a causal relationship between paternity and feather coloration and demonstrates that paternity allocation is dynamic between successive breeding attempts in this population of barn swallows.

Other nonexperimental studies have also reported differences in extrapair paternity rates between breeding bouts (*16*), providing further support for our finding that individuals rapidly adjust paternity in relation to mate quality. For example, male savannah sparrows (*Passerculus sandwichensis*) that provide high-quality parental care in a first brood receive greater paternity from their social mates in the subsequent breeding attempt (*17*).

Successive breeding bouts within the same pair bond and asynchronous breeding dates among breeding pairs are common in many socially monogamous species, suggesting that there should be a premium on the maintenance of ornamental traits even after pair bonds are formed. Indeed, the quality of ornaments including feather coloration (*18*, *19*) often declines within a breeding season, and other kinds of ornaments such as antlers or elongated plumes are subject to breakage and deterioration. Whether some males are better at maintaining their ornaments throughout a breeding season remains largely unknown.

Although the precise mechanism of paternity allocation was not tested in this study, mate choice and intrasexual competition may both have affected paternity outcomes (*2*, *20*–*22*). Females may exhibit some control over extrapair partner choice and fertilizations (*23*), and in European barn swallows there is experimental evidence for female choice of extrapair males with the longest tail streamers (*7*). However, it is also possible that males in our study with experimentally enhanced plumage prevented their mates from copulating with other males in the population. Melanin-based plumage color, like that exhibited by barn swallows (*24*), is used in other animals as an honest signal of dominance (*25*, *26*). Moreover, it is possible that both female choice and male-male competition favor the use of plumage color as a quality indicator in barn swallows, as has been discovered in recent experiments of melanin-based coloration in common yellowthroats, *Geothlypis trichas* (*27*). Lastly, it is possible that misrecognition of one's previous mate may have influenced the outcome of our experiment. However, sexually selected coloration in barn swallows (*13*) does not possess characteristics of traits typically used as signals of individual identity, such as discrete color morphs that do not signal reproductive performance (*28*). Additionally, many other characteristics of each male that could signal identity (e.g., song) were not manipulated in our experiment.

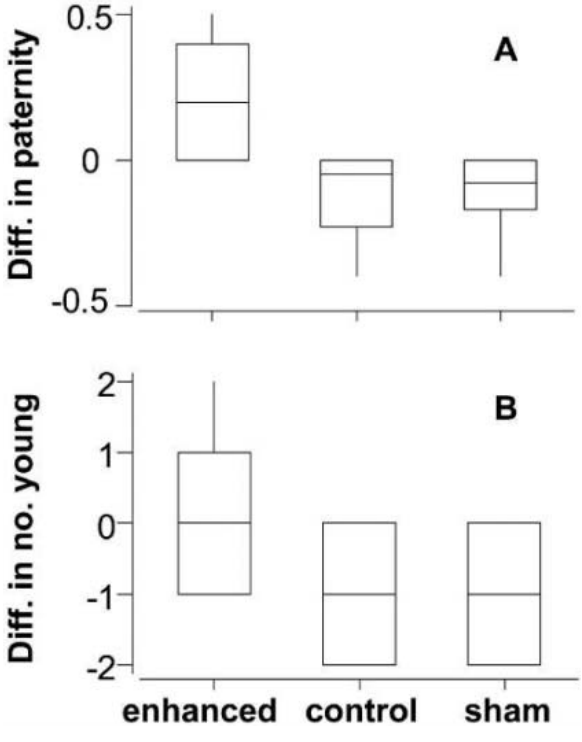

Fig. 2. (**A**) Differences in paternity for the replacement broods minus paternity for the first breeding attempts demonstrate that males whose coloration was enhanced gained more paternity, whereas males in both control groups lost or received no changes in paternity of young within their own nest. (**B**) Differences in the number of young sired by the focal male indicate that only males whose coloration was enhanced had greater numbers of their own offspring in replacement clutches, whereas males in both control groups had reduced numbers of their own offspring in replacement clutches. In these box and whiskers plots, whiskers indicate lines that extend from the bottom and top of the box to the lowest and highest values adjacent to the box that are defined by the following limits: lower limit = [quartile 1 − 1.5(quartile 3 − quartile 1)] and upper limit = [quartile 3 + 1.5(quartile 3 − quartile 1)].

Whether the underlying mechanism is governed by female choice, male-male competition, or both, the allocation of greater paternity to males with experimentally enhanced plumage color, despite the fact that all females remained paired with their original social males, is consistent with the hypothesis that flexibility in paternity allocation is a direct response to changes in male coloration, indicating that individuals use this signal to gauge important aspects of a male's quality. Although there are no previous demonstrations of dynamic paternity allocation decisions in relation to male ornaments, it is easy to posit strong selection on the flexibility of these decision rules because the pursuit of extrapair matings by both males and females has been shown to have important fitness outcomes (*2*–*6*). Moreover, dynamic decision rules are evident within the context of male paternal care and paternity certainty in species where extrapair matings are prevalent (*29*, *30*), suggesting that flexibility and dynamic assessment in allocation decision rules is an important component of variable reproductive strategies.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/309/5744/2210/DC1
Materials and Methods
Fig. S1
Table S1

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Transmembrane Protein GDE2 Induces Motor Neuron Differentiation in Vivo

Meenakshi Rao and Shanthini Sockanathan*

During neural development, coordinate regulation of cell-cycle exit and differentiation is essential for cell-fate specification, cell survival, and proper wiring of neuronal circuits. However, the molecules that direct these events remain poorly defined. In the developing spinal cord, the differentiation of motor neuron progenitors into postmitotic motor neurons is regulated by retinoid signaling. Here, we identify a retinoid-inducible gene, *GDE2* (glycerophosphodiester phosphodiesterase 2), encoding a six-transmembrane protein that is necessary and sufficient to drive spinal motor neuron differentiation in vivo. A single amino acid mutation in the extracellular catalytic domain abolishes protein function. This reveals a critical role for glycerophosphodiester metabolism in motor neuron differentiation.

During development of the nervous system, cell-cycle exit is coupled to cellular differentiation programs to ensure that correct numbers of neuronal subtypes are generated to construct functional neural circuits (*1*). This complex process involves the synchronized decrease in expression of progenitor determinants, the increase of cell-cycle inhibitors, and the implementation of defined cell-fate specification programs. The molecular mechanisms that coordinate and regulate these pathways remain unclear.

Spinal motor neuron generation in the chick requires the integration of three different extrinsic signals: sonic hedgehog, fibroblast growth factors, and retinoic acid (RA) (*2*, *3*). All three signaling pathways have been implicated in initial dorsal-ventral patterning of progenitor domains in the spinal cord (Fig. 1A). However, RA signaling is also necessary for the induction of oligodendrocyte transcription factor 2 (Olig2) in progenitors and their subsequent differentiation into postmitotic motor neurons (Fig. 1A) (*2*). When motor neuron progenitors differentiate, they decrease expression of Olig2 as they migrate out of the ventricular zone (VZ) and increase expression of postmitotic motor neuron markers such as islet1 and islet2 (Fig. 1A) (*4*). Olig2 has a pivotal role in motor neuron differentiation. It is required for the maintenance of a motor neuron progenitor state, and its down-regulation is essential for the implementation of neurogenic and motor neuron specification pathways (*5*, *6*).

Because the differentiation of motor neuron progenitors is dependent on retinoid signaling, we conducted a differential subtraction screen with cDNAs derived from ventral spinal cord explants grown in the presence or absence of retinol to identify genes involved in this process (Fig. 1B) (*7*). Probing reverse Northern blots with cDNAs from both sets of explants demonstrated that expression of clone 45.1 was increased about 50-fold in explants exposed to retinol compared with that of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Fig. 1C). Furthermore, in situ hybridization analysis revealed that clone 45.1 was expressed within or directly adjacent to developing tissues that synthesize RA, such as the spinal cord, paraxial mesoderm, mesonephros, heart, lung, and eye (fig. S1) (*8*). Sequence analysis revealed that clone 45.1 is a chick gene (AY910750) encoding a predicted protein of 599 amino acids with 67% identity to the human predicted protein PP1665 and 66% identity to mouse glycerophosphodiester phosphodiesterase 2 (GDE2) (*9*, *10*) (fig. S2), suggesting clone 45.1 is the chick homolog of GDE2. These proteins all contain a glycerophosphodiester phosphodiesterase (GDPD) domain, known to be involved in glycerophosphodiester metabolism (*11*). Analysis of the Conserved Domain Database revealed that GDE2 is a member of a large, heterogeneous family of GDPD-containing proteins for which in vivo functions are largely unknown (*9*). GDE2 is a transmembrane protein, and epitope tagging studies demonstrated that the GDPD domain is extracellular with intracellular localization of the N- and C-termini (fig. S3).

GDE2 is highly expressed by all somatic spinal motor neurons, irrespective of their rostrocaudal position, from the time they are generated (Fig. 2, A to F) until at least Hamburger-Hamilton (HH) stage 29 (*8*). These data are consistent with the induction of GDE2 expression by paraxial mesoderm-derived RA signaling. In order to determine when GDE2 might act in motor neuron development, the onset of GDE2 expression was examined. The differentiation of motor neuron progenitors can be monitored accurately by the

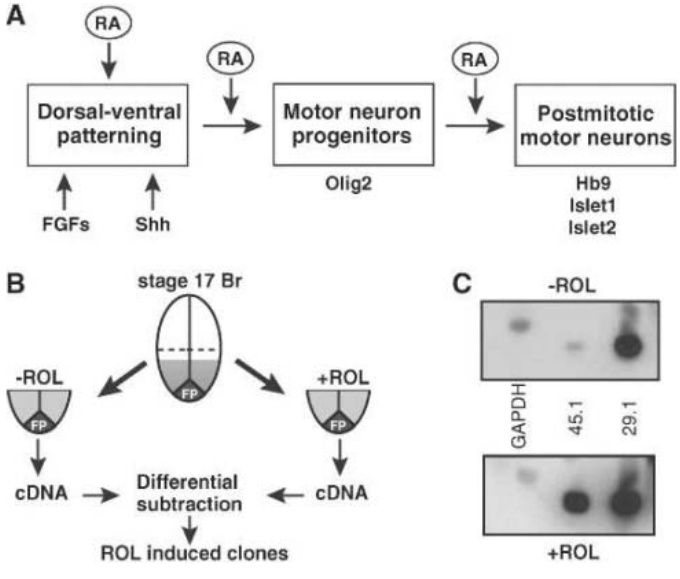

Fig. 1. GDE2 isolation and characterization. (**A**) Schematic depicting requirement for RA signaling at three distinct steps in motor neuron generation. Shh, Sonic hedgehog; FGFs, fibroblast growth factors. (**B**) Subtractive screen to isolate retinoid-responsive genes in motor neurons. Br, brachial neural tube; FP, floor plate; ROL, retinol. (**C**) Reverse Northern blots showing RA responsiveness of clone 45.1 when probed with cDNA from explants grown in the presence or absence of ROL compared with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and a non-RA-responsive clone, 29.1.

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sequential expression of molecular markers as well as the position of their cell bodies along the medial-lateral axis of the spinal cord. Actively cycling motor neuron progenitors located in the VZ of the spinal cord express large amounts of the transcription factor NK-homeobox 6.1 (Nkx6.1) and Olig2 (*4*, *6*) (Fig. 2G). These progenitor markers are extinguished as the cells exit the cell-cycle, migrate laterally, and begin to express motor neuron-specific transcription factors such as homeobox factor 9 (HB9), islet1, and islet2 (*4*) (Fig. 2G). GDE2 was localized in postmitotic, laterally located neurons that also expressed HB9, islet1, and islet2 (Fig. 2H) (*8*) but was not detected in medially located progenitor cells that expressed Nkx6.1 and Olig2 (Fig. 2, I and J). However, an intermediate population of cells weakly stained for Nkx6.1 and Olig2 also contained GDE2, suggesting that GDE2 expression may be initiated as cells transition to a postmitotic state (Fig. 2, I and J, arrows).

Once ventral neuronal progenitors undergo their terminal mitosis at the medial margin of the VZ, resulting daughter cells migrate laterally into the intermediate zone (IZ) (*12*). In the IZ, they increase expression of the cyclin-dependent kinase inhibitor p27 (*13*), undergo cell-cycle arrest, and respond to signals that trigger terminal differentiation (Fig. 2G). In embryos incubated with bromodeoxyuridine (BrdU), GDE2 was not detected in any cells that incorporated BrdU or were stained by the antibody MPM-2 (*14*), indicating that GDE2 is not expressed by progenitors undergoing S or M phase in the VZ (Fig. 2, K and L). The border between the VZ and the IZ is defined by S-phase nuclei labeled by BrdU (*12*). Lateral to this border, there was a subset of BrdU-labeled cells that expressed Olig2 as well as GDE2 (Fig. 2, K and M). Consistent with their location in the IZ, these cells contained small amounts of the cell-cycle inhibitor p27 (Fig. 2N). In summary, GDE2 was primarily expressed by mature motor neurons; however, its expression was initiated within cells in the IZ as they differentiated into postmitotic motor neurons.

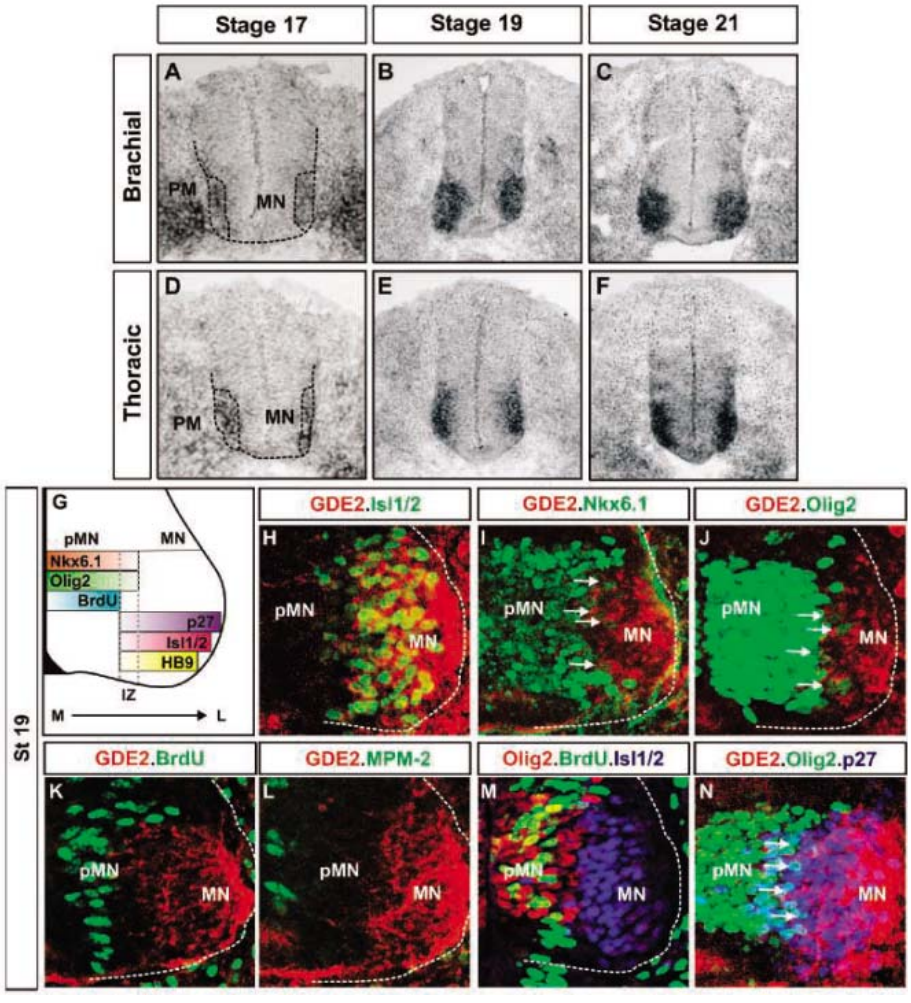

Fig. 2. GDE2 expression in spinal motor neurons. (**A** to **F**) In situ hybridization of *GDE2* mRNA in sections of chick spinal cord from limb (brachial) and nonlimb (thoracic) levels. Dotted lines mark the margins of the spinal cord and the motor neuron domain (MN). PM, paraxial mesoderm. (**G**) Schematic of molecular marker expression in ventral spinal cord. Arrow indicates medial (M) to lateral (L) axis. Dotted lines outline the intermediate zone (IZ). pMN, motor neuron progenitor domain. (**H** to **N**) Expression of GDE2 and molecular markers in HH stage 19 chick spinal cords. Ventral right quadrants are shown; medial is to the left and lateral to the right. Arrows in (I), (J), and (N), respectively, highlight cells that weakly stain for Nkx6.1, Olig2, or p27 and express GDE2 (BrDU, 30 min incubation). Dashed lines outline the margins of the spinal cord. Isl1/2, islet 1 and islet 2.

To test whether GDE2 might mediate the retinoid-dependent differentiation of Olig2 progenitors, we ablated GDE2 expression in the spinal cord by in ovo electroporation of small interfering RNAs (siRNAs) (*15*). All experiments used a green fluorescent protein (GFP) reporter plasmid to identify the electroporated side of the spinal cord. Electroporation of GDE2 siRNA typically resulted in a 70% loss of GDE2 mRNA and protein in spinal motor neurons (Fig. 3, A to C). Loss of GDE2 expression depended on the amount of siRNA administered, and siRNAs directed against different parts of the GDE2 open reading frame and 3′ untranslated region resulted in a similar loss of GDE2 mRNA and protein (fig. S4) (*8*). GDE2 silencing was not triggered by unrelated siRNAs, and GDE2 siRNAs did not induce global changes in gene expression (figs. S4 and S5). No toxicity was detected by terminal deoxynucleotidyl transferase biotin–deoxyuracil triphosphate (dUTP) nick end labeling (TUNEL) (*15*).

Embryos lacking GDE2 were analyzed for expression of the postmitotic motor neuron markers HB9, islet1, and islet2 by immunohistochemistry on the same or serial sections. In all cases a marked decrease in the number of neurons expressing each of these markers was evident on the electroporated side of the spinal cord, with about 70% loss of HB9-expressing neurons and 30 to 40% loss of more mature motor neurons expressing islet2 (Fig. 3, D and E, and fig. S5). Mice lacking HB9 show a progressive loss of islet1-expressing cells while they maintain normal numbers of islet2-expressing motor neurons, suggesting that separate pathways of motor neuron differentiation may exist (*16*, *17*). Our observation that GDE2 silencing affects HB9 expression more severely than islet2 indicates a differential requirement for GDE2 activity in these two pathways. We found no expansion in the number of neighboring interneurons, but an increase in TUNEL together with a reduction in the width of the electroporated ventral spinal cord was observed (Fig. 3, A to C) (*8*). These results provide evidence that GDE2 silencing results in the loss of postmitotic motor neurons and that cells destined to become motor neurons likely do not convert to a different fate but instead undergo cell death.

To confirm that the loss of motor neurons upon GDE2 silencing did not result from defects in progenitor generation or proliferation, we analyzed expression of the progenitor marker Olig2 and that of the ventral patterning genes paired box 6 (Pax6), Nkx2.2, and Nkx6.1 in embryos electroporated with GDE2 siRNA. There was no

change in the dorsal-ventral boundaries of the motor neuron progenitor domain or in the number of cells expressing Olig2 (fig. S5). Consistent with this, there was also no change in the number of cells expressing motor neuron restricted 2 (MNR2), a transcription factor turned on by committed progenitors in the S phase of the final cell cycle and maintained throughout their differentiation (*8*, *14*). Thus, GDE2 silencing appears not to affect progenitor cell generation or number.

To test whether GDE2 is sufficient to drive motor neuron differentiation, we misexpressed GDE2 throughout the spinal cord including within cycling Olig2-expressing progenitors in the VZ. We engineered a bicistronic construct with GDE2 linked to an internal ribosomal entry site (IRES) upstream of a nuclear form of β-galactosidase (GDE2NLZ) under the control of the chick β-actin promoter. Electroporation of GDE2NLZ into chick spinal cords resulted in high coincident expression of GDE2 and NLZ along the entire mediolateral axis in both progenitors and postmitotic neurons (Fig. 4, A and B). In contrast to the unelectroporated side, many medial cells in the electroporated VZ expressed the motor neuron marker HB9 (Fig. 4, C and D). Furthermore all of these medial HB9-containing cells also expressed markers of terminal motor neuron differentiation, such as islet2 (Fig. 4E) and choline acetyltransferase, the enzyme required for biosynthesis of the motor neuron neurotransmitter acetylcholine (*8*, *18*). To quantify this effect, we divided the ventrolateral spinal cord into three bins that roughly corresponded to domains of motor neuron progenitors, differentiating motor neurons, and postmitotic motor neurons (Fig. 4F). More islet2-expressing neurons were detected in bin 1 and bin 2 of embryos electroporated with GDE2NLZ than in embryos electroporated with NLZ alone (Fig. 4G). However, similar numbers of NLZ-expressing cells were detected in each case (Fig. 4).

Cells differentiating in response to GDE2 within the VZ expressed large amounts of the cell-cycle inhibitor p27 and failed to incorporate BrdU (Fig. 4, H to K). Moreover, these islet2-expressing cells in the VZ had decreased expression of Sry-related HMG box 1 (Sox1) and Sox2, transcription factors required for maintenance of neural progenitor status (*8*, *19*, *20*). Lastly, GDE2NLZ-electroporated embryos showed a corresponding loss of Olig2 within the VZ, and no cells expressing both Olig2 and islet2 were detected (Fig. 4E). However, the motor neurons generated in response to GDE2 misexpression were confined to the dorsal-ventral limits of the domain containing Olig2-expressing progenitors, suggesting a prior requirement for Olig2 expression in these cells (Fig. 4E). Promoting cell-cycle exit in the developing spinal cord is not sufficient to elicit terminal differentiation of motor neurons (*19*, *21*). Our results demonstrate that GDE2 is not only capable of driving cell-cycle exit but can coordinately down-regulate progenitor determinants and promote the differentiation of motor neuron progenitors into mature motor neurons.

The presence of the GDPD domain in GDE2 supports the possibility that its catalytic activity may be required for its function. The related two-transmembrane protein GDE1 can hydrolyze glycerophosphoinositol (GPI); GPI-4, 5-bisphosphate; and glycerophosphoserine; and this activity is dependent on the integrity of the GDPD domain (*9*). The GDPD domain of GDE1 is 51% similar to the catalytic X domain of phosphoinositide phospholipase C (PI-PLC) (*22*) (fig. S6), and three amino acids essential for PI-PLC catalytic activity are conserved (*23*, *24*). One of these three amino acids, a histidine, is also crucial for GDE1-mediated hydrolysis of GPI (*9*). Because the location of this histidine residue is conserved in the GDPD domain of GDE2 (fig. S6), we altered it to alanine (GDE2H.A) and determined whether the mutated protein could still promote ectopic motor neuron differentiation. Electroporation of GDE2H.ANLZ resulted in many electroporated cells within the VZ that expressed both NLZ and GDE2 (Fig. 4, L and M). However, no motor neurons expressing islet2 were detected (Fig. 4N). Transfection of GDE2H.ANLZ into human embryonic kidney–293 cells revealed no difference in amount of expression or membrane localization compared to transfection of GDE2NLZ (fig. S7). Thus, a single amino acid change within the putative catalytic site of the GDPD domain in GDE2 is sufficient to abolish the ability of GDE2 to promote motor neuron differentiation, providing strong evidence that GDPD activity is required for GDE2 function.

The extracellular orientation of the GDPD domain raises the possibility that it may act non-cell-autonomously. To test this idea, we electroporated GDE2NLZ into chick spinal cords and analyzed the number of ectopic motor neurons expressing NLZ. If GDE2 can function non-cell-autonomously, a fraction of the HB9-expressing neurons in bin 1 (Fig. 4F) should be untransfected and lack both NLZ and GDE2 expression. Although 85% of the HB9-containing cells in bin 1 did express NLZ, 15% did not but were in direct contact with GDE2-expressing cells (fig. S8). Thus, GDE2 function appears to be primarily cell-autonomous but may also be non cell-autonomous locally, at high con-

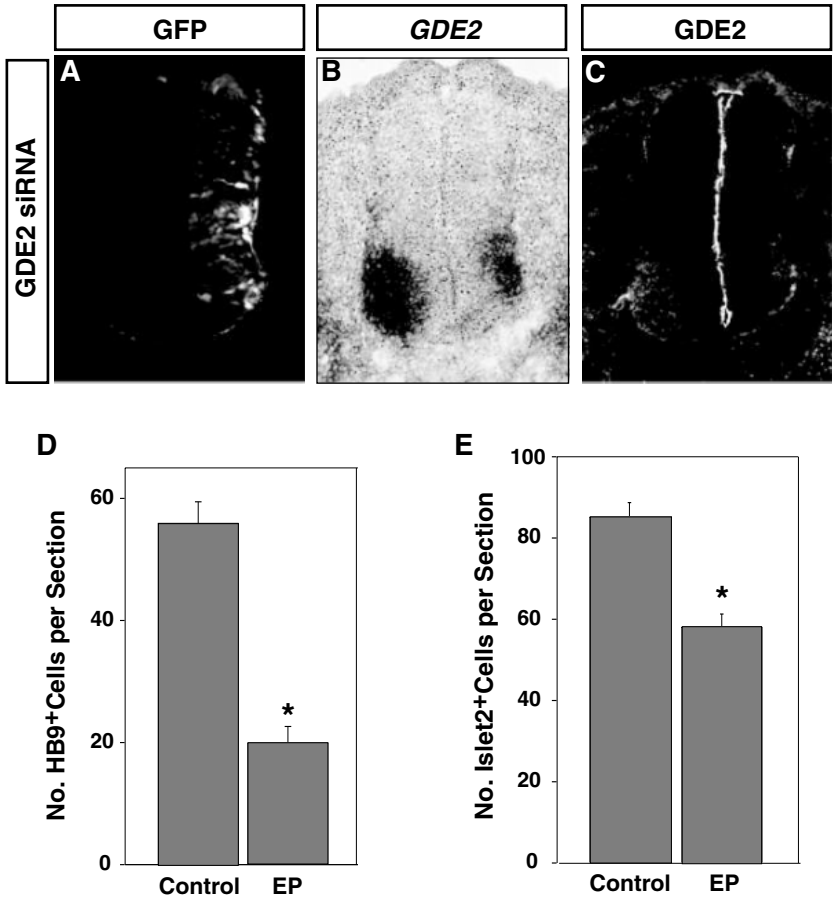

Fig. 3. Requirement for GDE2 in motor neuron differentiation. Right side of the spinal cord is electroporated. (**A** to **C**) *GDE2* mRNA (B) and protein (C) expression after electroporation of GDE2 siRNA. (**D**) Quantitation of HB9-expressing cells in electroporated (EP) and non-electroporated (control) sides of the spinal cord (n = 5, mean ± SEM). Asterisk indicates $P < 0.00000001$ (Student's t test). (**E**) Quantitation of islet2-expressing cells in electroporated (EP) and non-electroporated (control) sides of the spinal cord (n = 6, mean ± SEM). Asterisk indicates $P < 0.00000006$ (Student's t test).

centrations. Consistent with this, spinal cord explants grown in media conditioned by GDE2-expressing cells do not exhibit premature motor neuron differentiation (*8*).

We propose that paraxial mesoderm-derived RA induces expression of GDE2 in cells poised to differentiate into postmitotic motor neurons. The GDPD activity of GDE2 is required for its ability to promote cell-cycle exit and motor neuron differentiation, and this may result directly from reducing amounts of Olig2 (*5*). The extracellular location of the GDPD domain distinguishes it from other known proteins involved in lipid signaling (*22*), but the downstream pathways are unknown. One possibility is that GDE2 could act in concert with G-protein signaling pathways by analogy to GDE1, which interacts with members of the RGS (regulators of G-protein signaling) family of proteins (*25*). A related protein GDE3 induces the differentiation of osteoblast-like cell lines in vitro (*26*), raising the possibility that six-transmembrane GDPD-containing proteins may constitute a family of critical cell differentiation factors.

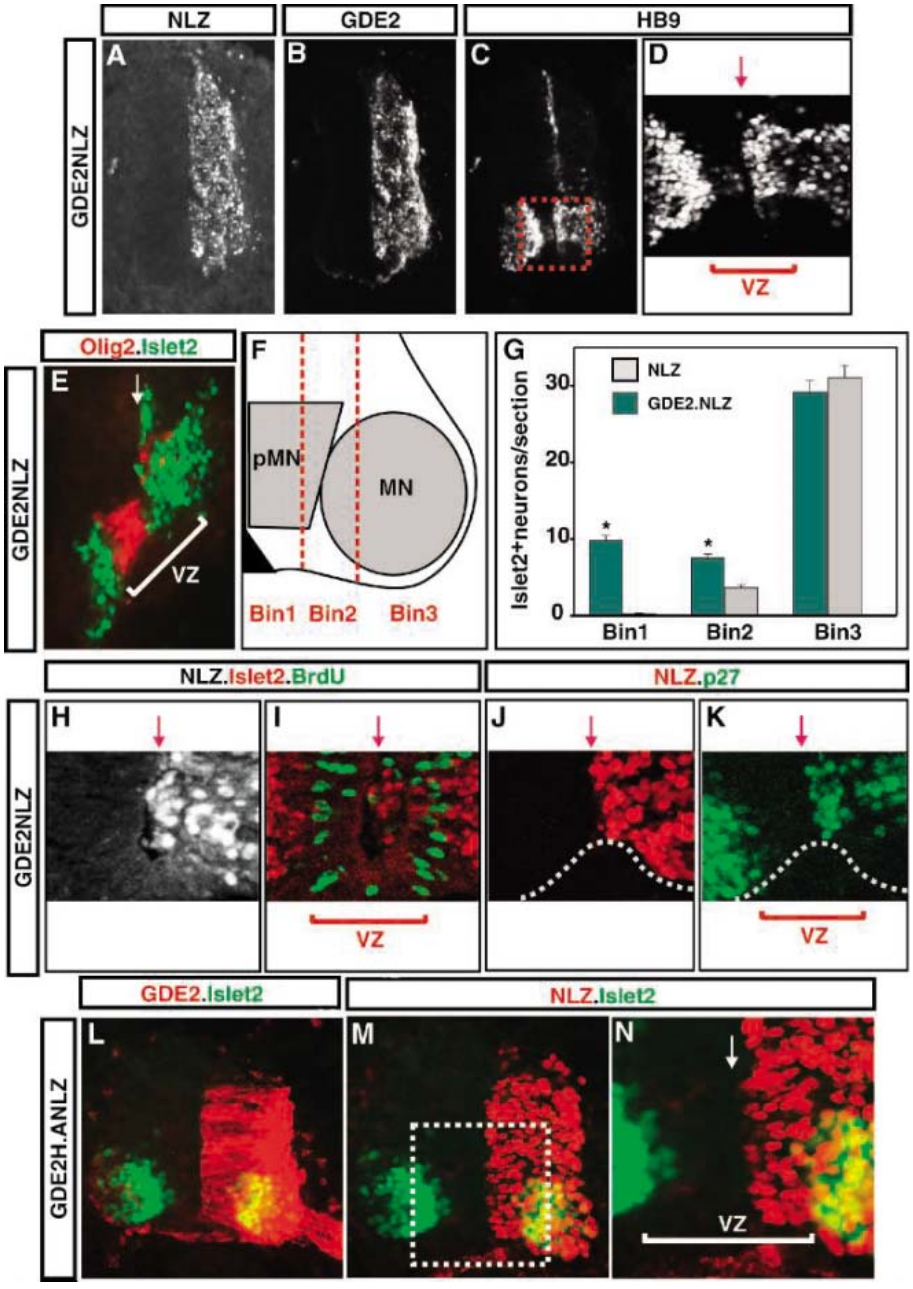

Fig. 4. Premature motor neuron differentiation induced by misexpression of GDE2. Arrows mark midline of spinal cord. Right side of the spinal cord is electroporated. (**A** to **D**) HB9 expression within the ventricular zone (VZ) after electroporation of GDE2NLZ. Boxed area in (C) is enlarged in (D). (**E**) Islet2 and Olig2 expression within the VZ after electroporation of GDE2NLZ. (**F**) Diagram of the ventral spinal cord divided into three bins: Bin 1 and bin 2 are about 20 μm wide and encompass Olig2$^+$ and Olig2$^+$/MNR2$^+$/HB9$^+$ domains, respectively. Bin 3 consists predominantly of HB9$^+$ and islet2$^+$ neurons. pMN, motor neuron progenitor; MN, motor neuron. (**G**) Number of islet2-expressing neurons located in bins 1 to 3 of embryos electroporated with GDE2NLZ versus NLZ alone (mean ± SEM, $n = 6$). With use of a Student's t test to evaluate each pair, differences between GDE2NLZ and NLZ in bins 1 (asterisk, $P < 0.00000001$) and 2 (asterisk, $P = 0.0000004$) are significant but not in bin 3 ($P = 0.396$). The total number of NLZ-staining cells is the same in both cases [bin 1: GDE2NLZ, 23 ± 1 (SEM);NLZ, 25 ± 1; asterisk, $P < 0.5$, $n = 6$] (**H** and **I**) Lack of BrdU incorporation by ectopic islet2-expressing neurons generated upon GDE2NLZ electroporation. (**J** and **K**) p27 expression within the VZ after electroporation of GDE2NLZ. Dotted lines outline the spinal cord. (**L** to **N**) Islet2 expression within the VZ after electroporation of mutant GDE2H.ANLZ. Boxed area in (M) is enlarged in (N).

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Tryptophan 7-Halogenase (PrnA) Structure Suggests a Mechanism for Regioselective Chlorination

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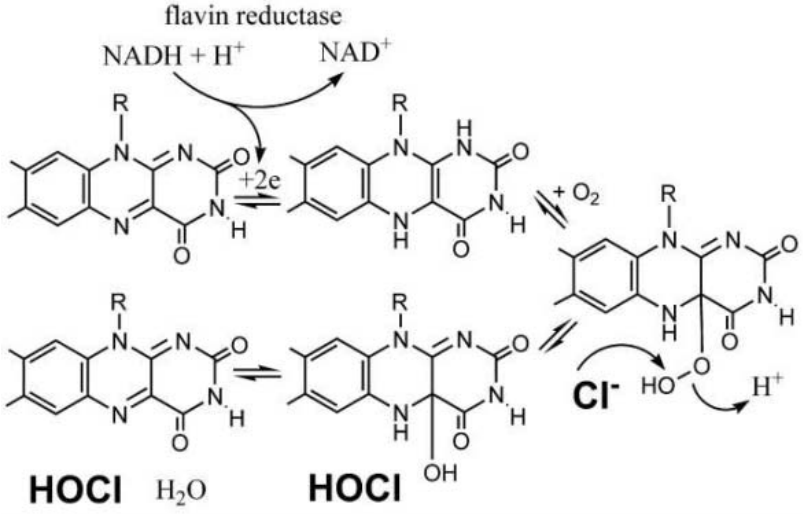
Chlorinated natural products include vancomycin and cryptophycin A. Their biosynthesis involves regioselective chlorination by flavin-dependent halogenases. We report the structural characterization of tryptophan 7-halogenase (PrnA), which regioselectively chlorinates tryptophan. Tryptophan and flavin adenine dinucleotide (FAD) are separated by a 10 angstrom–long tunnel and bound by distinct enzyme modules. The FAD module is conserved in halogenases and is related to flavin-dependent monooxygenases. On the basis of biochemical studies, crystal structures, and by analogy with monooxygenases, we predict that $FADH_2$ reacts with O_2 to make peroxyflavin, which is decomposed by Cl^-. The resulting HOCl is guided through the tunnel to tryptophan, where it is activated to participate in electrophilic aromatic substitution.

In addition to man-made chemicals, there are nearly 4000 chlorinated and brominated natural products (*1*), including drugs such as vancomycin (*2*), rebeccamycin (*3*), and cryptophycin A (*4*). The de novo chemical synthesis of complex natural products is often too expensive or too difficult to be practical. Their production relies on fermentation, and introducing diversity in such molecules requires protein engineering. This has been hampered by a lack of understanding of the molecular basis of the biological regioselective halogenation mechanism.

Metal-dependent haloperoxidases were once thought to catalyze all halogenation reactions in biology and fall into two classes. Both heme-iron-dependent enzymes (*5*) and vanadium-dependent enzymes (*6*) have been structurally characterized. Although different in structure, both form a metal-bound hydrogen peroxide, which reacts with halide ions to produce a metal-bound hypohalite ion. This ion dissociates from the metal as hypohalous acid (*5*, *6*), where in solution it reacts with substrate. Such halogenation lacks regioselectivity and substrate specificity (*7*). Perhydrolases are now recognized not to be involved in halometabolite biosynthesis (*8*). A new halogenase was reported by Dairi *et al.* identifying the gene for the chlorinating enzyme in chlorotetracycline biosynthesis (*9*). The gene product showed no similarity to haloperoxidases. Studies of the antifungal compound pyrrolnitrin from *Pseudomonas fluorescens* identified two related genes (*prnA* and *prnC*), coding for two halogenating enzymes (*10*) (fig. S1). Both contain a flavin binding site (*9*–*13*) and exhibit weak sequence homology to flavin-dependent monooxygenase enzymes (*14*). PrnA catalyzes the regioselective chlorination of the 7 position of tryptophan (*15*). Turnover requires that FAD is reduced to $FADH_2$ (by flavin reductase) and that O_2 is present (*11*). Members of this halogenase superfamily have been identified in the biosynthetic pathways of the antibiotics balhimycin (*16*) and vancomycin (*2*), the antitumor agent rebeccamycin (*3*), and other halometabolites (*7*, *17*–*21*). It is likely that regiospecific halogenation reactions carried out by bacteria are predominately catalyzed by flavin-dependent halogenases. To account for the regioselectivity, two mechanisms have been proposed. In one, the substrate is oxidized to an epoxide, which is decomposed by a nucleophilic attack of Cl^- (*11*). In the other, direct chlorination by a high-energy flavin hypochlorite intermediate occurs (*22*, *23*). The use of HOCl as the halogenating agent has been explicitly discounted because of its reactivity and regioselectivity (*11*, *23*).

PrnA was purified from a *P. fluorescens* expression system, and its structure was determined to 1.95 Å. The structure consists of residues 2 to 518 (Fig. 1A) and is a dimer (fig. S2A). Each monomer is a single domain, shaped like a box with a triangular pyramid stuck to one face (Fig. 1A). The box, which we identify as the FAD binding module, is dominated by two large β sheets (Fig. 1A). FAD is bound in a solvent-exposed groove adjacent to the large parallel β sheet (Fig. 1A). The C4-N5 edge of the isoalloxazine ring sits above one face of the mainly antiparallel β sheet (Fig. 1, A and B). Sequence alignment shows that only the flavin binding module is conserved in flavin-dependent halogenases (fig. S3). Conserved residues map to this module, and some of these residues are conserved in the monooxygenase enzymes (fig. S3). The flavin binding module of PrnA is structurally similar to *p*-hydroxybenzoate hydroxylase (PHBH) (*24*), a monooxygenase (fig. S4).

Cl^- is bound in a pocket on one face of the isoalloxazine ring (Fig. 1B) and makes contacts with the amide nitrogen atoms of Thr^{348} (T348) and Gly^{349} (G349) (*25*). No other Cl^- is experimentally located despite the presence of 50 mM NaCl, and we identify this as the Cl^- binding site. The amide backbone is known to bind negative ions and is proposed to bind F^- ion in the fluorinase structure (*26*). Complexes with tryptophan and 7-chlorotryptophan were obtained by incubating the protein, before



Scheme 1.

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crystallization, with each. Tryptophan (Fig. 1C) and 7-chlorotryptophan (fig. S5B) are bound by the pyramid, which we denote as the substrate binding module (Fig. 1A). The protein structures are similar, with the compounds bound in an essentially identical manner. The discussion focuses on the higher resolution tryptophan complex. There is no substantial change in the protein structure upon tryptophan binding; the most notable difference is increased disorder in the loop between β2 and α2 at G48, adjacent to the isoalloxazine ring (fig. S5C). FAD and Cl^- are bound at the same positions as in the native enzyme. One face of the tryptophan ring stacks against H101 and W455 (*25*), the other face against F103 (Fig. 1C). The indole nitrogen is hydrogen bonded to the backbone carbonyl of E346. The amino group of tryptophan makes a salt link with E450 and hydrogen bonds to other residues. The carboxylate group is also hydrogen bonded to the protein (Fig. 1C). We have obtained an $FADH_2$ structure by reducing the enzyme with dithionite. The crystals, obtained in the absence of Cl^-, have an empty Cl^- binding site. The isoalloxazine ring is bent and slightly changes its interaction with surrounding residues (fig. S5, C and D). The loop at G48 undergoes a conformational change, and the helices capping the tryptophan binding site become disordered (fig. S5C). Together with the observation that in substrate and product complexes the G48 loop is less well ordered, it suggests there is communication between the modules regulating the enzyme.

The mechanism of flavin-dependent monooxygenases is well established (*27*, *28*). These enzymes are reduced to give $FADH_2$, which then binds molecular oxygen to form a spectroscopically characterized highly reactive peroxide-linked flavin (*27*, *28*). This intermediate is decomposed by the nucleophilic attack of an adjacent phenolate substrate, resulting in oxygen atom transfer. Consistent with this established mechanism (*27*, *28*), we and others (*11*, *23*) propose that in PrnA $FADH_2$ binds O_2, forming the same peroxide-linked isoalloxazine ring (Scheme 1). There is no moiety in PrnA that appears capable of binding or interacting with O_2 other than $FADH_2$. In PrnA unlike PHBH, there is no room for an organic molecule to bind adjacent to the isoalloxazine ring, and the substrate is 10 Å distant. We see no indication of a large conformation change that could bring tryptophan and flavin together. Furthermore, the Cl^- ion binding site is over 10 Å from 7-chlorotrytophan and no other Cl^- binding site has been located. These observations seem to disfavor mechanisms involving direct transformation of substrate by oxygen linked to flavin (*11*) or flavin hypochlorite (*22*, *23*). We cannot entirely eliminate these mechanisms because large conformational changes could take place. However, we postulate that the chlorinating agent created from flavin peroxide moves 10 Å to the tryptophan. In PrnA, Cl^- is bound on the opposite face of FAD from the solvent and near to the entrance of the tunnel leading to the tryptophan (Fig. 1B). Cl^- is positioned to make a nucleophilic attack on the flavin peroxide, resulting in the formation of hydroxylated FAD and

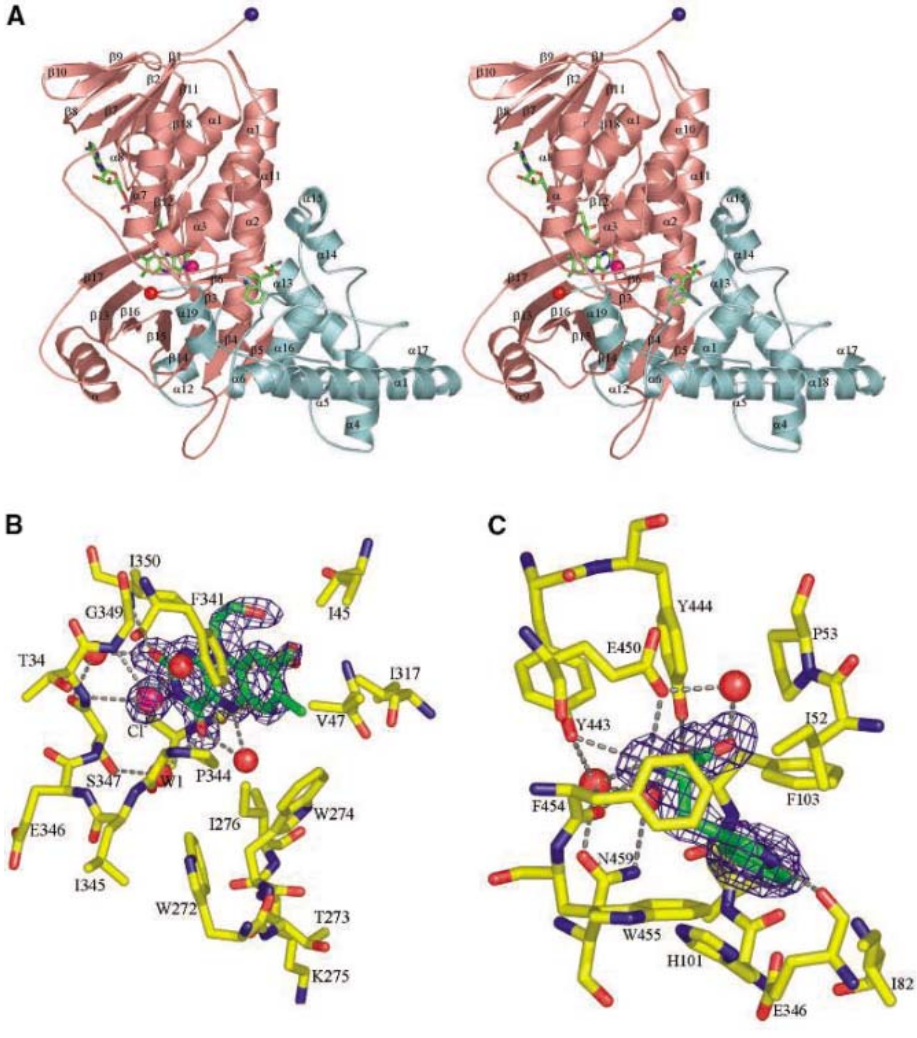

Fig. 1. (**A**) Stereoimage of the monomer of PrnA, a flavin-dependent halogenase; secondary structure elements are numbered (*25*). Residues 1 and 519 to 538 are disordered. The N terminus is denoted by a blue sphere and C terminus by a red one. FAD and 7-chlorotryptophan are shown as sticks; carbon, green; oxygen, red; nitrogen, blue; chlorine, purple; and phosphorus, magenta. The Cl^- ion is shown as a pink sphere. The box-shaped flavin binding module (residues 1 to 102 and 159 to 401) is colored salmon and has dimensions of 30 Å by 30 Å by 60 Å. The pyramid-shaped substrate module (residues 103 to 158 and 402 to 518) is colored cyan; each side of the pyramid is about 35 Å. The flavin binding module has two large β sheets, one parallel consisting of β1, β2, β7, β11, and β18 at the top of the figure and one mainly antiparallel β4, β5, and β13 to β17 at the bottom of the figure. In addition, it has two smaller β sheets (β8 to β10 and β3 and β6) and an α-helical bundle (α1 to α3 and α7 to α11). The substrate binding module is entirely helical (α4 to α6 and α12 to α19). (**B**) The FAD and Cl^- ion binding sites. The figure is oriented 180° around the vertical axis relative to (A). An unbiased Fo-Fc map is contoured at 3σ (blue) and at 8σ (cyan). Only the isoalloxazine of FAD is shown for clarity. A stereo version of the figure and the full molecule are shown in fig. S2, B and C. The Cl^- ion is at over 10σ in the Fo-Fc map. In the protein molecule, carbon atoms are colored yellow, all other atoms are colored as in (A), and water molecules are shown as red spheres. One water molecule (labeled W1) is conserved in all structures, and its relationship to the mechanism is discussed. Hydrogen bonds are shown as dotted lines. The isoalloxazine ring has essentially the same interaction with the protein in all structures. (**C**) The substrate binding site. An unbiased Fo-Fc map contoured at 3σ is shown for the tryptophan substrate. Atoms are colored as in (B). The interactions with the protein are identical for 7-chlorotryptophan (the product). All residues within 4 Å of tryptophan are shown and labeled. A stereo version of the figure is shown as fig. S5A.

HOCl (Scheme 1). The formation of HOCl from peroxides is well known in chemistry. Close to the expected site of this reaction, a water molecule is hydrogen bounded to S347 (Fig. 1B).

PrnA incubated with 5-methylindole results in the formation of 3-chloro-5-methylindole (*29*) (fig. S6). We have established that, in solution, the substrate mimic 5-methylindole reacts with HOCl to give 3-chloro-5-methylindole (fig. S7). In order to confirm the enzyme reaction was not due to adventitious HOCl production, we tested PrnA for its ability to chlorinate monochlorodimedone (MCD). MCD, which is much more reactive than 5-methylindole, is chlorinated by free HOCl and is used to assay haloperoxidases (*5*, *30*) (fig. S6). MCD does not inhibit and is not chlorinated by PrnA (fig. S8), indicating that MCD does not access the tryptophan binding site. It establishes that production of 3-chloro-5-methylindole by enzyme does not arise from the presence of HOCl in solution. 5-Methylindole inhibits PrnA, consistent with it accessing the tryptophan binding site. The chlorinating agent at the tryptophan site has identical reactivity to that of HOCl (with respect to 5-methylindole). These data are consistent with the proposal that HOCl is created and channeled by PrnA. Modeling suggests PrnA binds 5-methylindole orienting its 3 position toward the tunnel (fig. S9). We propose HOCl is generated by the conserved flavin binding module and is therefore general to all flavin-dependent halogenases, irrespective of substrate or halogen (Cl or Br).

The 10 Å tunnel is lined by the polypeptide main chain and the side chains of residues I82, K79, I52, and S347 (*25*) (Fig. 2A). These would not be oxidized or chlorinated by HOCl. W272 and W274 are remote from the site of HOCl formation, and, in any event, on its own tryptophan is not chlorinated by HOCl (*23*). We suggest that HOCl, after formation, is prevented from diffusing into solvent by the protein structure and instead enters this tunnel, moving toward tryptophan. In the native PrnA structure, K79 makes a hydrogen bond with a water molecule located at the end of the tunnel adjacent to the Cl atom of 7-chlorotryptophan (Fig. 2A). K79 may hydrogen bond to HOCl and thus position it to react with tryptophan. In the absence of this water molecule, there is a cavity centered on the 7 position of tryptophan (Fig. 2A). We propose the basis for regioselective halogenation is the controlled spatial presentation of HOCl to substrate. There is a chemical precedent for this; in solution HOCl reacts with anisole resulting in *p*- and *o*- substitution. By first adding cyclodextrin, which is thought to wrap around anisole masking the *o*-positions, it has been shown that only *p*-substitution occurs (*31*).

Electrophilic addition of chlorine to tryptophan proceeds through a Wheland intermediate (Fig. 2B). This intermediate would be stabilized by interaction with E346, reminiscent of but reversed in polarity from π cation interactions (*32*, *33*). E346 is positioned to deprotonate the intermediate, leading to product (Fig. 2, A and B). Tryptophan is less reactive than other aromatics and in solution is not chlorinated by HOCl (*23*). A more electrophilic source of Cl than HOCl is known to be required (*23*). If K79 does hydrogen bond to HOCl, it would activate Cl by increasing its electrophilicity (Fig. 2B), allowing it to chlorinate tryptophan. Such a spatially constrained activating step may not only accomplish halogenation of less reactive substrates but could protect nearby tryptophan residues. In our assay, the native enzyme has a low k_{cat} of 0.1 min^{-1} (fig. S10); however, rebeccamycin halogenase is also slow with a k_{cat} of 1.4 min^{-1} (*23*). We find no detectable activity for a K79→A79 mutant, consistent with K79 playing a key role in guiding and activating HOCl. The k_{cat} for PrnA E346Q (an E346→Q346 mutant) is decreased by about two orders of magnitude; K_M is unchanged (fig. S11). This supports our proposed role for E346 (Fig. 2B) in stabilization and deprotonation of the intermediate. Halogenation using HOCl is well known in nature and organic chemistry, yet it lacks the reactivity and regioselectivity required for biosynthetic pathways. We suggest that with halogenases biology has evolved a remarkable mechanism of generating, activating, and controlling HOCl.

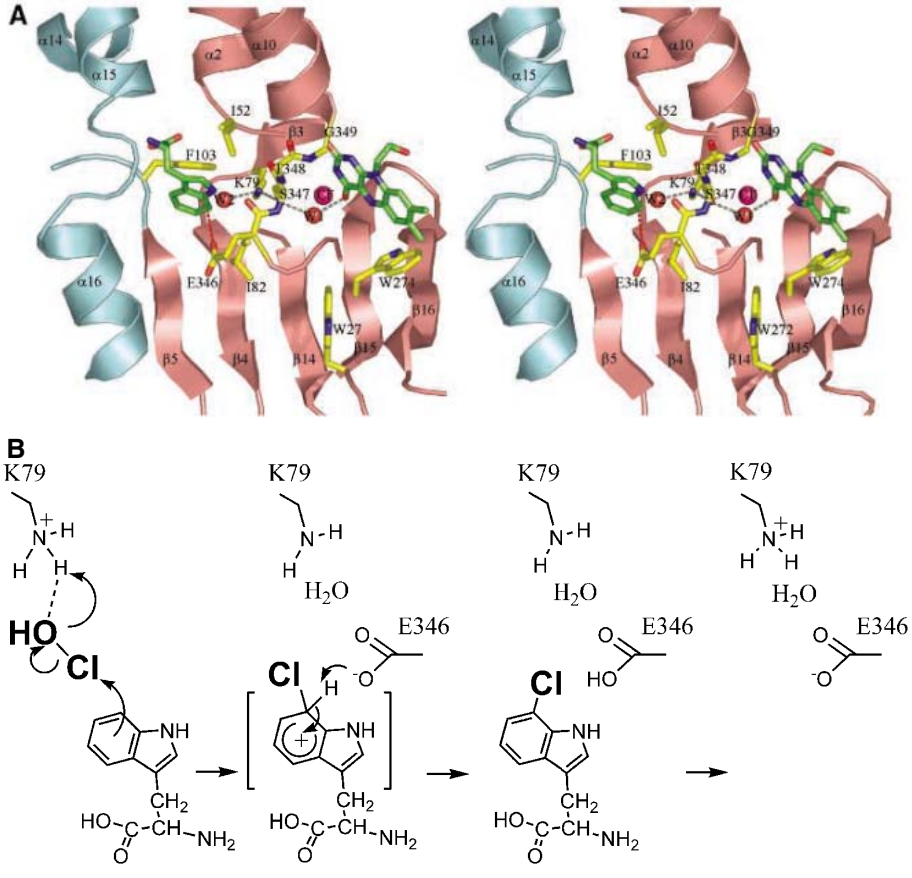

Fig. 2. (**A**) A tunnel connects the FAD and tryptophan binding sites. The side chain of T348 (*25*) is omitted and only a truncated FAD molecule is shown for clarity. Part of the protein structure is removed for clarity; secondary structure elements are labeled. W1, shown as a red sphere, is found in all structures. W2 is a second water molecule found only in the native structure. It has been placed in this image to illustrate the path through the tunnel in the protein that we suggest HOCl follows from Cl^- to substrate. W2 is absent in both co-complexes because it would sterically clash with ligand. The interaction of E346 with the 7 position of tryptophan is shown as a red dotted line. (**B**) Halogenation of tryptophan proceeds by electrophilic aromatic substitution at the 7 position. The Wheland intermediate is shown in square brackets and would be stabilized by interaction with E346. K79 in the apo structure makes three hydrogen bonds, suggesting a polar environment for the NZ atom, consistent with a protonated NZ atom. The indole ring stacks with W455 and H101 on one face and F103 on the other, which may further stabilize the intermediate.

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25. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
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Rev1 Employs a Novel Mechanism of DNA Synthesis Using a Protein Template

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The Rev1 DNA polymerase is highly specialized for the incorporation of C opposite template G. We present here the crystal structure of yeast Rev1 bound to template G and incoming 2′-deoxycytidine 5′-triphosphate (dCTP), which reveals that the polymerase itself dictates the identity of the incoming nucleotide, as well as the identity of the templating base. Template G and incoming dCTP do not pair with each other. Instead, the template G is evicted from the DNA helix, and it makes optimal hydrogen bonds with a segment of Rev1. Also, unlike other DNA polymerases, incoming dCTP pairs with an arginine rather than the templating base, which ensures the incorporation of dCTP over other incoming nucleotides. This mechanism provides an elegant means for promoting proficient and error-free synthesis through N^2-adducted guanines that obstruct replication.

Rev1, a member of the eukaryotic Y family DNA polymerases, is highly specific for incorporating a C opposite template G (*1*, *2*). In this respect, Rev1 differs not only from the replicative and repair polymerases (Pols), which incorporate the correct nucleotide opposite all four template bases with nearly equivalent catalytic efficiencies, but it differs

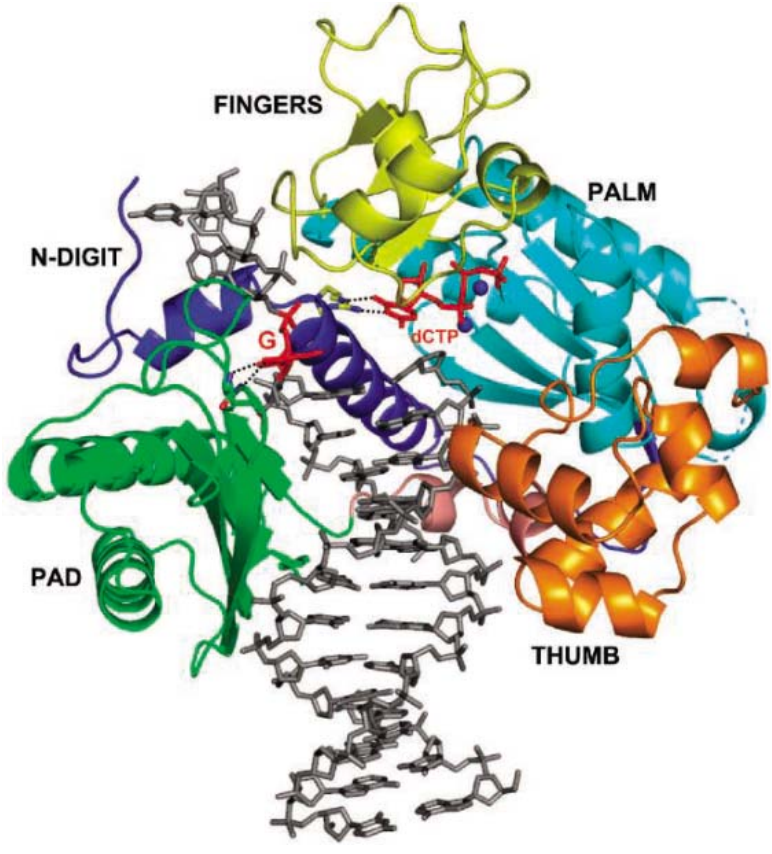

Fig. 1. Structure of the Rev1-DNA-dCTP ternary complex. The palm, fingers, and thumb domains and the PAD are shown in cyan, yellow, orange, and green, respectively. The linker joining the thumb to the PAD is shown in pink. The N-digit in Rev1 is shown in dark blue. DNA is in gray, template G and incoming dCTP are in red, and the putative Mg^{2+} ions are in dark blue. Black dashed lines depict hydrogen bonds between dCTP and Arg^{324}, and between template G and a loop in the PAD. Cyan dashed line indicates an unstructured loop in the palm domain.

also from the other three eukaryotic Y family Pols—η, ι, and κ (*3*). Of these, Pols η and κ form the four Watson-Crick base pairs with similar catalytic efficiencies (*4–6*), whereas Polι incorporates the correct nucleotide opposite template purines with a much higher efficiency than opposite template pyrimidines (*7–11*).

Rev1 incorporates a C opposite template G with an efficiency (k_{cat}/K_m) of 1.2 μM^{-1} min^{-1}, and it misincorporates a G, an A, or a T opposite template G with efficiencies that are lower by a factor of about 10^3 to 10^5 than for the incorporation of C (*2*). Rev1 also incorporates a C opposite templates A, T, and C with efficiencies that are lower by a factor of about 10^2 to 10^3 than for the incorporation of C opposite template G; moreover, Rev1 shows no propensity for incorporating the correct nucleotide opposite these template residues (*2*). Rev1 incorporates a C opposite an abasic site also, albeit with a lowered efficiency compared with that opposite template G (*2*). Rev1, thus, is specific not only for template G, but also for the incoming 2′-deoxycytidine 5′-triphosphate (dCTP) (*2*). Furthermore, Rev1 can proficiently incorporate a C opposite an N^2-adducted G, for example, a γ-hydroxy-1,N^2-propano-2′-deoxyguanosine (γ-HOPdG) adduct generated from the reaction of acrolein (produced by the peroxidation of lipids in cells) with the N^2 of a G (*12*).

The specificity of Rev1 poses two questions. First, what is the chemical basis for Rev1's G-template specificity? Second, what is the chemical nature of Rev1's specificity for incorporation of a C nucleotide, even opposite an abasic site?

We report here the structure of the Rev1 catalytic core (residues 297 to 746), which exhibits the same nucleotide incorporation specificity and efficiency as the wild-type protein, in ternary complex with a template-primer presenting G in the active site and with incoming dCTP (table S1). The structure, determined at 2.3 Å resolution (fig. S1), reveals Rev1 embracing the template-primer with its palm (residues 356 to 365, 438 to 536), fingers (366 to 437), and thumb (537 to 603) domains, and the PAD (polymerase-associated domain; residues 621 to 738) unique to Y family polymerases (*13–18*) (Figs. 1 and 2). The palm carries the active site residues (Asp^{362}, Asp^{467}, and Glu^{468}) that catalyze the nucleotidyl transfer reaction. The fingers domain lies over the replicative end of the template-primer, but, unlike other DNA polymerases it makes very few contacts with the templating base; instead, interactions are primarily with incoming dCTP and the unpaired nucleotides at the 5′ end of the template. The thumb and the PAD approach the template-primer from opposite sides, connected by a long linker, which is mostly helical rather than extended as in other Y family polymerases (Figs. 1 and 2). Incoming dCTP binds with its triphosphate moiety interlaced between the fingers and palm domains, making hydrogen bonds with Ser^{402}, Tyr^{405}, and Arg^{408} from the fingers domain and Lys^{525} from the palm domain (Fig. 3A). The catalytic residues, Asp^{362}, Asp^{467}, and Glu^{468} are arrayed between the dCTP triphosphate moiety and the primer terminus, and two Mg^{2+} ions—analogous to metals "A" and "B" in replicative DNA polymerases (*19–21*)—complete the Rev1 active site (Fig. 3A). Overall, Rev1 is well poised for dCTP insertion, with the putative 3′ oxygen (at the primer terminus) located ~4 Å from the dCTP α-phosphate and aligned with respect to the Pα-O3′ bond (angle of about 160°).

The right-handed grip of palm, fingers, thumb, and the PAD on the template-primer is augmented in Rev1 by an "N-digit" at the N terminus (305 to 355) that interacts with incoming dCTP. The N-digit is composed of a loose α-loop substructure that fits into a shallow depression at the confluence of the palm, fingers, and PAD, connected to a long α helix that travels between the palm and the PAD and joins at the base of the palm (Figs. 1 and 2). The Rev1 PAD is exceptional in having an extra-long loop, a "G loop," which interacts with template G. Compared with Polι-DNA-dNTP (2′-deoxynucleoside 5′-triphosphate) ternary complexes (*18*, *22*), the Rev1 PAD as a whole is shifted toward the 3′ end of the template, which both creates a "route" for the N-digit helix and helps to position the G loop (670 to 688) (Fig. 2A).

The templating G and incoming dCTP do not pair with each other. The templating G is evicted from the DNA helix by Leu^{325} (from

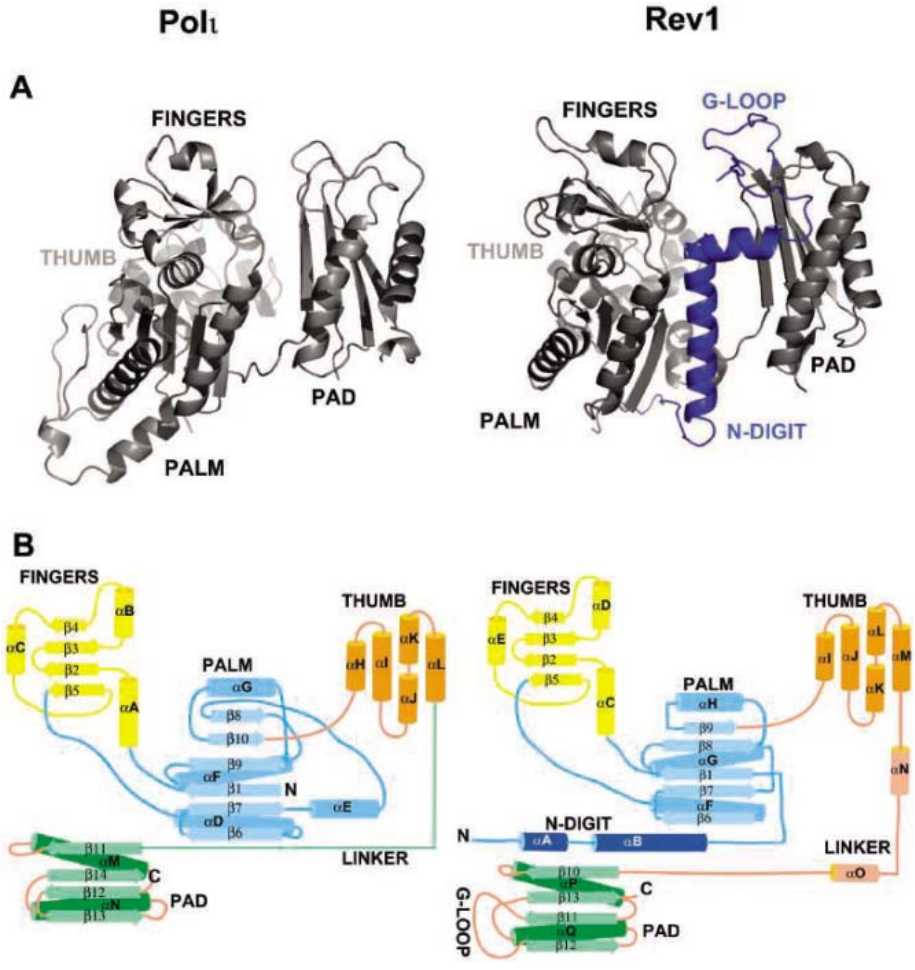

Fig. 2. Comparison between Rev1 and Polι. (**A**) The juxtaposition of structurally equivalent domains in Rev1 and Polι. The N-digit is unique to Rev1 and is highlighted in dark blue. Also highlighted in dark blue is an extended loop in the Rev1 PAD (termed the G loop) that interacts with template G. (**B**) Secondary structure and domain topologies of Rev1 and Polι. The coloring scheme is the same as in Fig. 1.

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the N-digit) jutting into the DNA (Fig. 3), reminiscent of the flipping of DNA bases in DNA methyltransferases and glycosylases (*23*). Leu[325] takes up much of the space vacated by templating G, whereas an adjoining residue, Arg[324], makes a set of complementary hydrogen bonds with incoming dCTP (Fig. 3). The dCTP base tilts toward Arg[324], whereas the dC base at the primer terminus tilts in the opposite direction to accommodate Leu[325] (and to a lesser extent Leu[328]) within the DNA helix. The N-digit is indispensable for Rev1 function, as the protein encompassing residues 329 to 746 is completely inactive. This protein lacks residues 305 to 328 of the N-digit, among which are the residues Arg[324] and Leu[325].

The templating G swings out of the DNA helix (at ~90°) and two hydrogen bonds are established between N7 and O6 at its "Hoogsteen edge" and the main-chain amides of Met[685] and Gly[686] on the G loop (Fig. 3). In addition, the O6 of G hydrogen bonds to a water molecule linked to Lys[681], and the N3 makes an out-of-plane hydrogen bond with a water molecule that is fixed in position by Asp[399], Trp[417], and Lys[681]. The pattern of hydrogen bonding is such that only a G can optimally pair with the G loop. If the templating G were to be replaced by A, for example, the N^6 of A would be incapable of making a hydrogen bond with the NH of Gly[686], and there would also be electrostatic and steric repulsion from the positioning of two hydrogen bond donors opposite each other. Similarly, T or C in place of G would again lead to a loss of hydrogen bonds; and in the case of T, the C5 methyl group would also sterically clash with the G loop. In view of these steric constraints, it is not surprising therefore that Rev1 prefers an abasic site at the templating position rather than an A, C, or T.

In addition to hydrogen bonds with the G-loop main chain, the extruded templating G is also fixed in its extrahelical position by a set of van der Waals contacts. The guanine slips into a small hydrophobic pocket delineated by the Met[685] side chain on one side and the aliphatic portion of Lys[681] on the other (Fig. 3). It is also noteworthy that Gly[686] occupies a region of the Ramachandran plot (ϕ = 66.0 and ψ = −163.1) more easily accessible to a glycine, which suggests that a glycine at this position is important in configuring the G loop. Taken together, the chemical basis for Rev1's G-template specificity is that the extrahelical G makes optimal hydrogen bonds with a segment of Rev1 instead of the incoming nucleotide.

Also, unlike other DNA polymerases, incoming dCTP pairs with an arginine rather than the templating base. Two hydrogen bonds are established between N3 and O^2 at the Watson-Crick edge of dCTP and the Nη2 and Nε donor

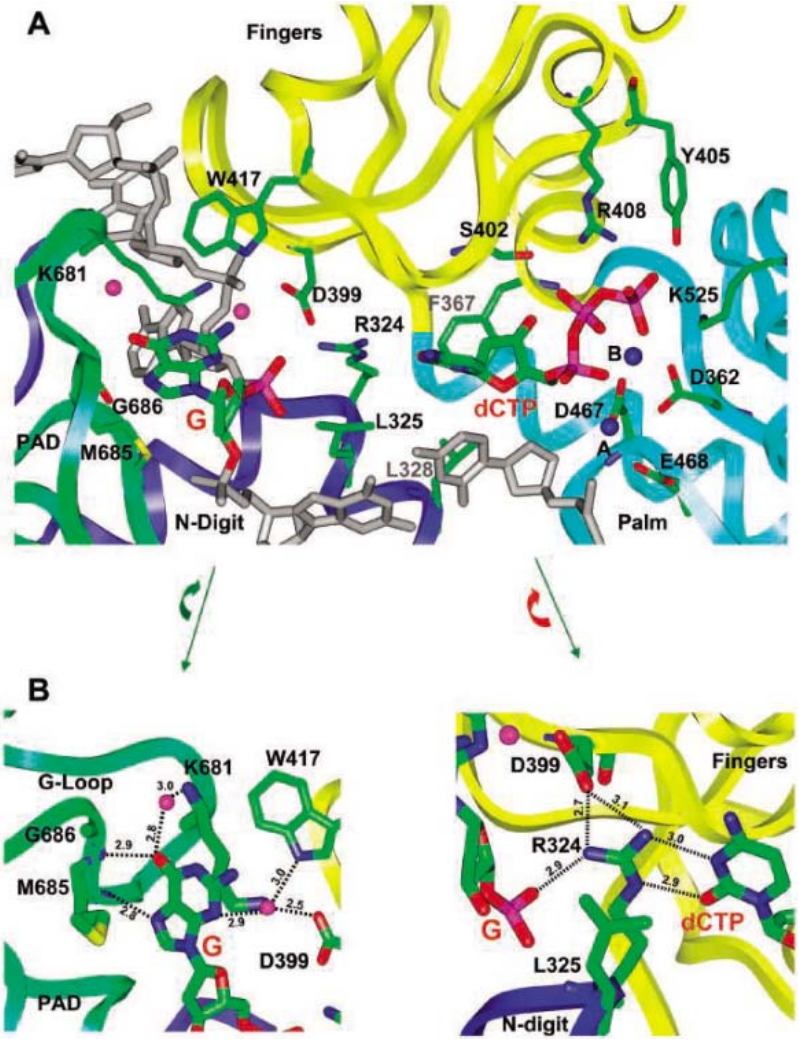

Fig. 3. Rev1-DNA-dCTP interactions. (**A**) A close-up view of the Rev1 active site region. The N-digit, fingers, and palm domains and the PAD are shown in dark blue, yellow, cyan, and green, respectively. The DNA is colored gray, and template G and incoming dCTP are shown in full atom coloring. The putative Mg^{2+} ions are dark blue, and the two displayed water molecules are colored magenta. Highlighted and labeled are the catalytic residues (*27*) (D362, D467, and E468), residues that interact with the triphosphate moiety of incoming dCTP (S402, Y405, R408, and K525), R324 that makes hydrogen bonds with dCTP base, L325 that pushes template G out of the DNA helix, and residues that interact with the extrahelical template G (M685, G686. K681, and W417). Note that template G and incoming dCTP partner with segments of Rev1. (**B**) Close-up views of template G–G-loop (left) and incoming dCTP-Arg[324] (right) interactions. Dashed lines depict the network of direct and water-mediated hydrogen bonds (with distances in angstroms above the bonds).

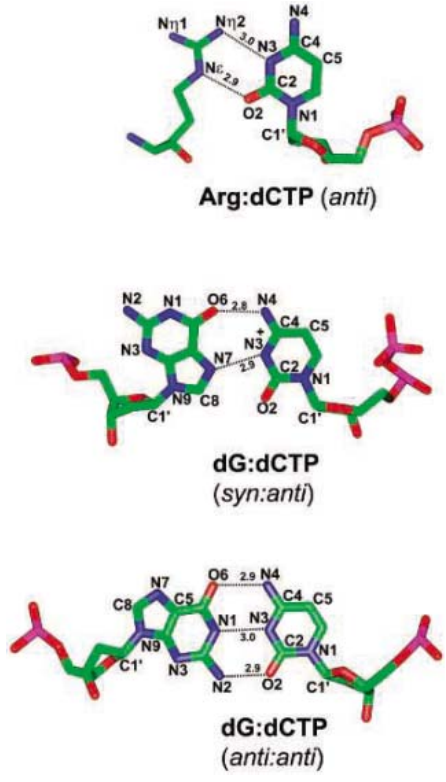

Fig. 4. Comparison between Arg:dCTP pairing in Rev1 (**top**), Hoogsteen dG:dCTP base-pairing in Polι (**middle**), and standard Watson-Crick dG:dCTP base-pairing in replicative DNA polymerases (**bottom**). The atoms and hydrogen bonding distances are labeled.

groups of Arg^{324}, respectively (Figs. 3 and 4). Arg^{324} extends from the N-digit and is buttressed as the surrogate templating residue by a network of hydrogen bonds with Asp^{399} and the 5′ phosphate of the ejected template G. The pattern of hydrogen bonding between dCTP and Arg^{324} is again such that substitution by any other incoming nucleotide would lead to loss of hydrogen bonds, as well as unfavorable electrostatic and steric intrusion. If dCTP were to be replaced by 2′-deoxythymidine 5′-triphosphate (dTTP), it would position two hydrogen bond donors opposite each other [N3-H(T)-H-Nη2(Arg^{324})], whereas substitution by dGTP or dATP would be even more severe, with the larger purine colliding with the guanidinium group of Arg^{324}. By pairing dCTP with an arginine, Rev1 maintains specificity for dCTP over other incoming nucleotides, even opposite an abasic site.

The structure suggests a specific mechanism for Rev1's ability to promote replication through N^2-adducted guanines that obstruct replication. The N^2 group of G can conjugate with a variety of endogenously formed adducts. Indeed, Rev1 has recently been shown to promote replication through an N^2-adducted G, derived from acrolein. Acrolein, an α,β-unsaturated aldehyde, is generated in vivo as the end product of lipid peroxidation and during oxidation of polyamines. The reaction of acrolein with the N^2 of G in DNA followed by ring closure at N1 leads to the formation of the cyclic adduct γ-HOPdG (fig. S2), which presents a strong block to synthesis by DNA polymerases. Rev1, however, incorporates a C opposite this lesion as efficiently as opposite an undamaged G (*12*). The exclusion of template G from the DNA helix places the N^2 of G in a large (solvent-filled) void between the PAD and the fingers domain (Fig. 3), where an adduct such as γ-HOPdG would be sterically unhindered (fig. S2). Indeed, one major role of Rev1 DNA synthetic activity based on an extrahelical G would be to promote replication through a variety of N^2-guanine adducts that sterically impinge on the minor groove. The incorporation of a correct nucleotide opposite an N^2-adducted guanine is ensured by the pairing of dCTP with an arginine. The structure also correlates well with the inhibitory effect that lesions such as O^6-methylguanine and 8-oxoguanine have on Rev1's ability to incorporate C (*2*). Unlike the N^2 group, the O^6 and C8 atoms are relatively buried when template G is evicted from the DNA helix, and almost any adduct at these positions will invariably clash with Rev1.

In the transfer RNA (tRNA) CCA-adding enzyme, both the tRNA backbone and the protein contribute to the specificity of the incoming nucleotide (*24*). The Rev1 structure presents a mechanism for DNA polymerization in which specificity for both the templating and the incoming nucleotide is provided by the protein rather than the DNA. Eukaryotic translesion synthesis polymerases thus use a variety of means of DNA polymerization, which include Watson-Crick base-pairing by Pols η (*25*) and κ (*26*), Hoogsteen base-pairing by Polι (*18*, *22*), and protein template–directed synthesis by Rev1 (Fig. 4).

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27. Single-letter abbreviations for the amino acid residues here are as follows: D, Asp; E, Glu; F, Phe; G, Gly; K, Lys; L, Leu; M, Met; R, Arg; S, Ser; W, Trp; and Y, Tyr.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/309/5744/2219/DC1
Materials and Methods
Figs. S1 and S2
Tables S1
References and Notes

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Experience-Driven Plasticity of Visual Cortex Limited by Myelin and Nogo Receptor

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Monocular deprivation normally alters ocular dominance in the visual cortex only during a postnatal critical period (20 to 32 days postnatal in mice). We find that mutations in the Nogo-66 receptor (NgR) affect cessation of ocular dominance plasticity. In $NgR^{-/-}$ mice, plasticity during the critical period is normal, but it continues abnormally such that ocular dominance at 45 or 120 days postnatal is subject to the same plasticity as at juvenile ages. Thus, physiological NgR signaling from myelin-derived Nogo, MAG, and OMgp consolidates the neural circuitry established during experience-dependent plasticity. After pathological trauma, similar NgR signaling limits functional recovery and axonal regeneration.

Central nervous system myelin proteins limit axonal growth and regeneration after traumatic and ischemic injury in adult mammals (*1–14*), but a physiological role for the myelin inhibitor pathway has not been defined. Ocular dominance (OD) within visual cortex provides a paradigm to study experience-dependent plasticity. Monocular deprivation of the contralateral eye induces a relative shift in ocular dominance of cortical responses toward the nondeprived ipsilateral eye (*15*). Both anatomical and electrophysiological studies in cats have defined a critical period during which the cerebral cortex is sensitive to experience-dependent plasticity, but after which altered visual experience does not change visual cortex responsiveness (*15–17*). In mice, single-unit recordings under barbiturate anesthesia have revealed a similar critical period for OD between 19 and 32 days postnatal (P19 to P32) (*18–20*). Although mouse OD plasticity measured with this method ceases after P32, a level of adult OD plasticity can be detected by other methods, such as immediate early gene expression and visually evoked potential field

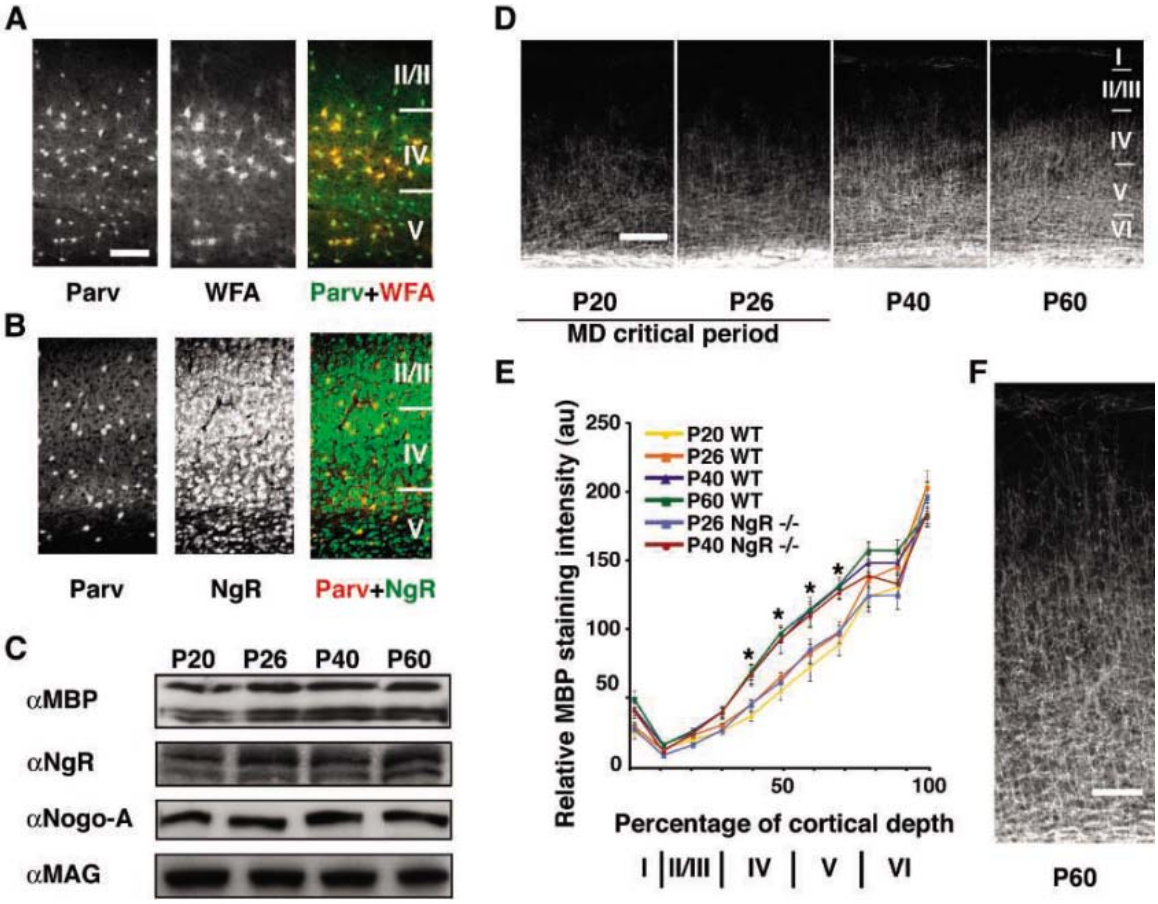

Fig. 1. Expression of myelin, NgR, and CSPG in mouse visual cortex during the critical period for OD plasticity. (**A**) P40 visual cortex labeled for parvalbumin (green in merge) and wisteria floribunda agglutinin (red in merge). (**B**) Sections as in (A), labeled for parvalbumin (red in merge) and NgR (green in merge). (**C**) Homogenates of visual cortex were immunoblotted with the indicated antibodies. Microdensitometry revealed that the concentration of any one protein varied by <20% across these ages, and there were no significant changes in protein levels with age. (**D**) P20 to P60 visual cortex labeled with antibodies to MBP. Layers I to VI are indicated (right). (**E**) Distribution of relative MBP intensity within visual cortex. (**F**) A higher magnification image of MBP distribution at P60. Error bars reflect SEM; $n = 3$ mice. Asterisks denote significant differences ($P < 0.05$) between P20 and P26 versus P40 and P60 for both genotypes. Scale bars in [(A) and (B)] = 100 μm, in (D) = 200 μm, and in (F) = 100 μm.

recordings (*19*, *21*–*23*). Adult plasticity is distinct from adolescent critical period plasticity. Adult plasticity relies on the slow onset of strengthened inputs from the nondeprived eye rather than a suppression of responses from the contralateral eye (*23*). Barbiturate anesthesia masks OD plasticity in adult but not juvenile mice (*22*). Plasticity achieved during the critical period is more persistent than that obtained in the adult (*22*). Here, we focus on the abrupt loss of OD plasticity at the end of the critical period in single-unit cortical recordings from anesthetized mice.

Previous investigations have revealed a critical role for parvalbumin-positive γ-aminobutyric acid (GABA)–ergic neurons in timing the critical period. Dark rearing impairs inhibitory circuit maturation (*24*) and delays the closure of the critical period (*25*). Genetic disruption of a GABA synthetic enzyme, glutamic acid decarboxylase 65 (GAD65), precludes OD plasticity (*26*). Brain-derived neurotrophic factor is thought to expedite critical period closure by maturing GABAergic neurons (*27*). Loss of dendritic spines correlates with OD plasticity and requires both GAD65 function and tissue plasminogen activator (tPA) (*28*).

Chondroitin sulfate proteoglycans (CSPGs) are astrocyte- and neuron-derived axon-outgrowth inhibitors that have also been implicated in OD plasticity. Infusion of chondroitinase ABC into spinal cord–injured animals cleaves glycosaminoglycan chains and promotes a degree of regeneration and functional recovery (*29*) comparable to that of Nogo/NgR antagonism (*8*, *11*). Injecting chondroitinase into adult rat visual cortex partially reactivates OD plasticity in response to monocular deprivation (*30*). To consider the cellular site of CSPG action, we examined wisteria floribunda agglutinin–stained sections of visual cortex. It is remarkable that CSPG-positive perineuronal nets predominantly (>85%) surround parvalbumin-positive inhibitory neurons, leaving nearly all other neurons unencumbered (Fig. 1A). Although genetic and pharmacological manipulation of cortical inhibition supports a model in which parvalbumin-positive inhibitory neurons initiate the critical period for OD plasticity (*31*, *32*), glutamatergic synapses also contribute substantially to OD plasticity (*33*). Both the incomplete extent of OD plasticity restoration by chondroitinase treatment and the GABA-restricted CSPG distribution led us to consider whether more widely distributed neurite-inhibiting mechanisms might participate in OD plasticity. As the vast majority of cortical neurons express NgR (Fig. 1B), we considered whether NgR-mediated myelin inhibition of neurite outgrowth contributes to closing the critical period.

Myelin-associated proteins, including ligands for NgR, are easily detected in postnatal visual cortex (Fig. 1C). The absolute abundance of the NgR ligands, Nogo-A and MAG, is essentially constant in homogenates of visual cortex over the time course of the critical period, whereas NgR tends to increase slightly (Fig. 1C). Similarly, levels of the compact myelin marker, myelin basic protein (MBP), increase only minimally during this period. A limitation of the immunoblot analysis is a mixing of all cortical layers such that selective expression changes in certain cortical layers most critical for plasticity may be obscured. Therefore, we used an immunohistochemical analysis of MBP between P26 and P60 to allow for a layer-specific assessment of expression. Although the total concentration of MBP remains

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nearly constant, layer-specific levels of intracortical myelin mature considerably as the critical period ends (Fig. 1D). At P20 and P26, the beginning and height of the critical period, respectively, the half-maximal staining intensity is obtained at 30% of the distance from the subcortical white matter to the pial surface, whereas after the end of the critical period, at P40 and P60, this measure of myelination extends significantly further, into 50% of the cortex ($P < 0.001$) (Fig. 1E). Within layers IV and V, the relative intensity of MBP staining increases by nearly 60% and 40%, respectively. The onset and distribution of cortical myelination in mice lacking NgR is indistinguishable from that of wild-type mice (Fig. 1E). Overall, the maturation of intracortical myelination correlates with the end of the critical period.

To assess OD plasticity, we first characterized the electrophysiological responsiveness of the binocular visual cortex in NgR mutant mice exposed to unmodified visual stimuli. NgR null mice have normal vision as assayed by receptive field azimuth distribution, receptive field size, response properties, and spontaneous activity (fig. S1, A to C). The weighted ocular dominance (WOD) scores for NgR mutants and wild-type mice are comparable (Fig. 2D).

To explore whether NgR regulates the magnitude of OD plasticity, we tested NgR mutant mice during the critical period. OD shifts in NgR mutant mice were induced by 4 days of monocular deprivation beginning at P24. The OD histograms and calculated WOD scores (Fig. 2A) are indistinguishable from the values for wild-type mice receiving monocular deprivation at the same age. Thus, visual system development and immature cortical plasticity are normal in the absence of NgR.

To investigate whether NgR participates in restricting OD plasticity in older animals, we deprived NgR mutants and wild-type littermates at P45, after the end of the critical period. Consistent with reported findings, 4 days of monocular deprivation do not induce an OD shift in wild-type mice (Fig. 2B). However, monocular deprivation of NgR mutant mice generates an OD shift (Fig. 2C) that differs significantly from the OD of either P45 nondeprived NgR mutant mice (Fig. 2D) or wild-type controls. Longer periods of monocular deprivation (8 days in one mouse) in NgR mutant mice beginning at P45 did not increase the magnitude of the OD shift. NgR is known to mediate myelin inhibition of neurite outgrowth; a simple model for enhanced P45 plasticity is a reduction in myelin inhibition of process growth. As the NgR ligand, Nogo-A, accounts for a considerable fraction of myelin inhibition of neurite outgrowth (*9*, *34*, *35*), a similar OD phenotype is predicted for mice lacking Nogo-A. Indeed, mice homozygous for a "gene-trap" insertion that eliminates expression of Nogo-A (and the related isoform Nogo-B) (*9*) display OD shifts following 4 days of monocular deprivation beginning at P45 (Fig. 2, E and F). The magnitudes of these shifts are identical to those observed with NgR mutants. Although myelinated fibers are more abundant in layers IV to VI, the OD scores from more superficial and deeper recording depths for a given penetration were indistinguishable in monocularly deprived NgR mutant mice at all ages tested.

OD plasticity at P45 in NgR and Nogo-A/B mutant mice, but not in wild-type mice, might be explained either by an absence of plasticity-limiting mechanisms or by a 2-week delay in developmental maturation of the visual cortex. Nissl staining and immunohistochemistry did not reveal any general deviation in the pace of brain development for these two strains from wild-type mice (Fig. 1). To determine whether OD plasticity persists into adulthood in NgR mutant mice, we examined mice at 4 months of age, roughly three times as old as mice at the end of the critical period. Four days of monocular deprivation is sufficient to induce OD shifts comparable to those observed in mice tested during the critical period (Fig. 2G). Therefore, a slight developmental delay in OD plasticity restriction cannot explain these findings, which indicates that NgR-dependent mechanisms participate directly in restricting visual cortex experience-dependent plasticity.

NgR signaling might function upstream in a plasticity cascade to regulate GABAergic maturation, neurotrophin levels, and/or tPA signaling. Alternatively, NgR may function downstream or

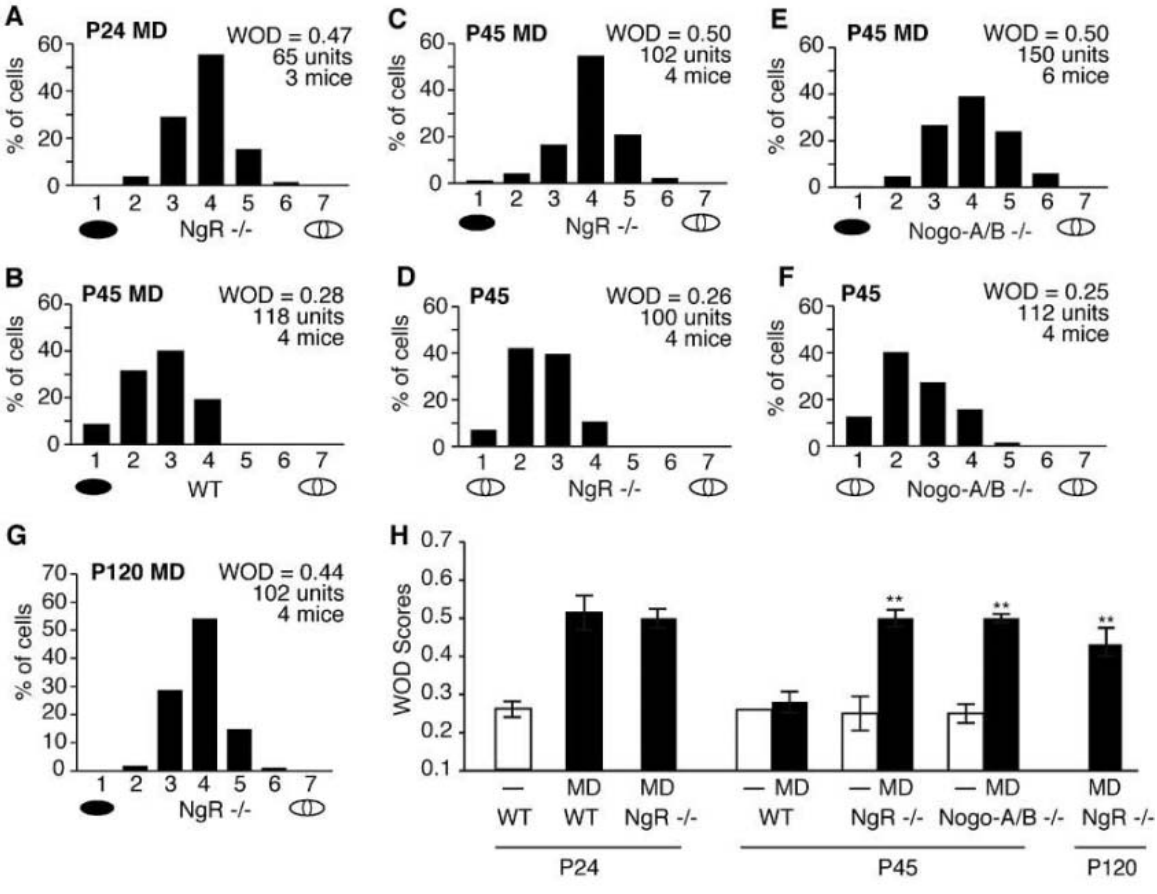

Fig. 2. NgR and Nogo-A/B mutant mice are sensitive to monocular deprivation after the critical period. (**A**) OD histogram and average WOD score for NgR mutant mice receiving monocular deprivation (black ellipse beneath the abscissa) at P24. (**B** to **G**) OD histograms and WOD scores as in (A), for wild-type (WT), NgR, and Nogo-A/B mutant mice with and without monocular deprivation. (**H**) Mean WOD scores for monocularly deprived and nondeprived animals across genotype and age. Bars represent the WOD values in [(A) to (G)]; error bars are SEM. Double asterisks denote significant differences ($P < 0.001$) of P45 and P120 WOD scores from P45 WT nondeprived and monocularly deprived scores.

independently of these mediators and limit anatomical rearrangements directly. To examine whether NgR regulates OD plasticity by modifying the GABAergic system or tPA-plasmin activity, we compared the expression of GAD65 and tPA protein in visual cortex from wild-type and NgR mutant mice (Fig. 3). Absence of NgR protein does not alter GAD65, parvalbumin, or tPA immunoreactivity in the visual cortex of P60 mice (Fig. 3, A to E), which suggests that NgR functions independently or downstream of these proteins to regulate plasticity. Dark rearing delays closure of the critical period by altering GABAergic neurotransmission (*24*) but does not alter the maturation of intracortical myelination, as indicated by MBP staining of sections of visual cortex in P40 mice or NgR levels (fig. S2, A and B). Thus, NgR signaling serves as a necessary gate on visual cortex plasticity. Although we cannot exclude the possibility that NgR signaling is modulated by GABA neurotransmission or tPA activity, our results support a model in which myelin and NgR function independently. These pathways presumably converge to regulate anatomical rearrangements in visual cortex.

The distribution of intracortical myelin and NgR is widespread (Fig. 1), so multiple neuronal subtypes have the potential to be regulated by this system. Given the prominence of GABAergic systems in ocular dominance plasticity, we examined the mouse visual cortex for myelinated GABAergic processes. Consistent with electron micrographs (*36*, *37*), roughly one-third of MBP-stained visual cortex fibers are parvalbumin-positive (Fig. 3H). Because the electrophysiological recordings presented here implicate myelin-associated inhibitors as regulators of OD plasticity, it will be interesting to examine whether the NgR pathway modulates primarily GABAergic connections, dendritic spine rearrangements, or other anatomical connections.

The current study provides genetic evidence for the hypothesis that myelination consolidates neural circuitry by suppressing plasticity in the mature brain. Specifically, NgR and Nogo-A/B are required for maturation-dependent restrictions on OD plasticity to monocular deprivation in the visual cortex. However, myelin is not the only limit on cortical plasticity, because CSPGs are also known to have a role in the visual cortex (*30*), and certain measures of OD persist in the adult mouse (*19*, *21*–*23*). Dark rearing delays the maturation of GABAergic neurons and the deposition of CSPGs into perineuronal nets (*30*) but does alter the maturation of intracortical myelination, which is controlled by developmental determinants not dependent on visual experience. Thus, at least two distinct inhibitors limit OD plasticity to the critical period, and eliminating either one is sufficient to facilitate plasticity.

The Nogo/NgR pathway is not required for closure of critical period plasticity throughout the cerebral cortex. Somatosensory barrel-field anatomical plasticity to whisker ablation is not significantly altered in Nogo-A/B mutant mice (fig. S2). Nonmyelin mechanisms may be relatively important in limiting barrel-field plasticity because the relevant critical period ends earlier in development (P1 to P4), before cortical myelination matures, or because barrel-field plasticity can be mediated subcortically (*38*).

Recovery of motor function after pathological damage to the mature brain is facilitated by structural and synaptic plasticity. The failure of surviving neurons to reestablish functional connectivity is most obvious after spinal cord injury, but limited axon regeneration and plasticity is central to the pathophysiology of a range of neurological disorders, including stroke, head trauma, multiple sclerosis, and neurodegenerative disease. The NgR-mediated response to myelin inhibitors is known to participate in limiting recovery from spinal cord injury and stroke (*8*, *10*–*12*). Thus, brain myelin proteins impede both physiological plasticity and the repair of pathologic injury by a shared NgR mechanism.

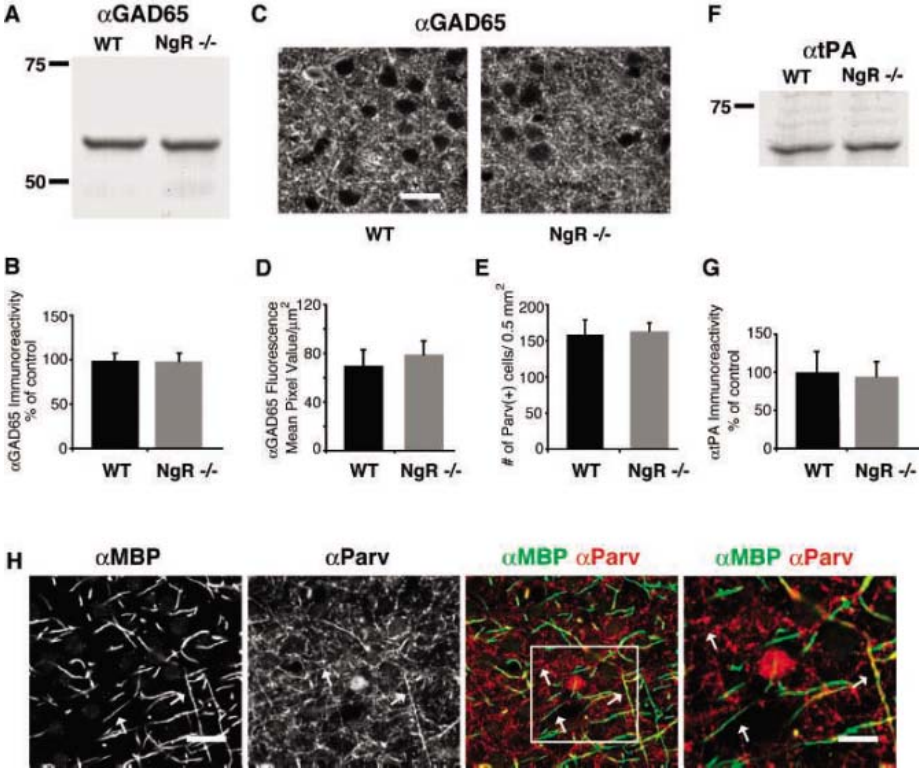

Fig. 3. GAD65 and tPA are normal in NgR mutant mice. (**A**) Homogenates of visual cortex from wild-type (WT) and NgR mice were immunoblotted with antibodies to GAD65. (**B**) Densitometry of GAD65 immunoreactivity from blots of P60 visual cortex from WT and NgR mutants (n = 4 mice). (**C**) P60 visual cortex of WT and NgR$^{-/-}$ mice labeled with antibodies to GAD65. (**D**) Microdensitometric level of GAD65 immunoreactivity in the neuropil of visual cortex from WT and NgR mutants. (**E**) Density of parvalbumin-immunopositive interneurons in visual cortex of WT and NgR mice, per 0.5 mm^2. (**F**) Immunoblot as in (A), with an antibody to tPA. (**G**) Quantification of tPA expression as in (B). (**H**) Confocal images of WT P60 visual cortex double-labeled with antibodies to MBP and to parvalbumin. White arrows point to immunopositive fibers in the αMBP and αParv panels, one that colocalizes in the merged image (right arrow) and others that do not (left and upper arrows). A higher magnification image, outlined by the white rectangle, is shown on the far right. Scale bar for [(C) and (H)] = 20 μm; for the higher magnification image, scale bar = 10 μm.

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Direct Evidence for a Parietal-Frontal Pathway Subserving Spatial Awareness in Humans

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Intraoperative electrical stimulation, which temporarily inactivates restricted regions during brain surgery, can map cognitive functions in humans with spatiotemporal resolution unmatched by other methods. Using this technique, we found that stimulation of the right inferior parietal lobule or the caudal superior temporal gyrus, but not of its rostral portion, determined rightward deviations on line bisection. However, the strongest shifts occurred with subcortical stimulation. Fiber tracking identified the stimulated site as a section of the superior occipitofrontal fasciculus, a poorly known parietal-frontal pathway. These findings suggest that parietal-frontal communication is necessary for the symmetrical processing of the visual scene.

Left unilateral neglect is a neurological condition resulting from right hemisphere damage (*1*, *2*). Neglect patients ignore left-sided events in everyday life (*3*) and have a poor functional outcome. They typically bisect horizontal lines to the right of the true center (*2*, *4*), perhaps because they perceive the left half of the line as being shorter or less salient than the right half (*5*, *6*). The study of unilateral neglect is important if we are to understand the mechanisms of spatial cognition, but its anatomical correlates are controversial. Most studies implicate the inferior parietal lobule (IPL) (*7*, *8*), consistent with the known role of posterior parietal cortex in spatial attention (*9*, *10*) and perceptual salience (*11*). Others implicate the rostral superior temporal gyrus (rSTG) (*12*), suggesting a segregation of spatial awareness in the ventral cortical visual stream (*13*, *14*). The underlying subcortical association circuits have received less attention (*15*).

We used intraoperative direct electrical stimulation (*16*) to study line bisection performance. During brain surgery for tumor resection, it is common clinical practice to awaken patients in order to assess the functional role of restricted brain regions (the brain has no receptors for pain), so that the surgeon can maximize the extent of the exeresis without provoking cognitive impairment. Patients perform cognitive tasks, such as counting or figure naming, while the surgeon temporarily inactivates restricted regions (~5 mm) around the tumor by means of electrical stimuli (*16*). If the patient stops talking or produces incorrect responses, the surgeon avoids removing the stimulated region.

CAL, a 27-year-old woman, and SB, a 28-year-old man, both left-handed, underwent surgical resection of a low-grade glioma (WHO II). In CAL, the glioma was centered on the caudal part of the right temporal lobe (*17*). CAL showed a rightward deviation upon stimulation of two cortical sites: the supramarginal gyrus (SMG, the rostral subdivision of the IPL) and the caudal portion of the superior temporal gyrus (cSTG) (Fig. 1) (table S2). There was no deviation during stimulation of the rSTG or of the frontal eye field.

In SB, the glioma was centered on the right inferior parietal lobule (*17*). SB showed a rightward deviation remarkably identical in amplitude to that shown by CAL (Fig. 2) (table S2) upon stimulation of the SMG. SB also deviated rightward during cSTG stimulation, again consistent with CAL's performance. Stimulation of other neighboring areas ("control 1" in Fig. 2B) did not determine pathological shifts. During tumor resection, subcortical regions on the floor of the surgical cavity were stimulated. SB showed a large rightward deviation upon stimulation of the restricted region labeled as 42 in Fig. 2A, but not of neighboring cortical or subcortical areas ("control 2" in Fig. 2B). Stimulation of region 42 was repeated after additional excavation of the surgical cavity, causing even greater deviations ("O-FF 2" in Fig. 2B). Again, stimulation of neighboring subcortical sites had no effect on line bisection performance. Still further extension of the resection into the depth of the angular gyrus caused SB to deviate rightward even during stimulation of neighboring regions, or in the absence of any stimulation ("control 3" in Fig. 2B). As a consequence, the neurosurgeon decided to stop the exeresis at this level. Five days after surgery, SB accurately bisected 20-cm lines ("day +5" in Fig. 2B) and showed no signs of neglect (table S1).

Using diffusion tensor magnetic resonance tractography (*18*) on postoperative magnetic resonance imaging (MRI) scans and diffusion tensor imaging (DTI) scans, we were able to precisely map the course of long association fibers in the white matter of this patient (*19*). The region labeled as 42 in Fig. 2A, whose inactivation had produced the maximal rightward shifts on line bisection, corresponded exactly to a portion of the superior occipitofrontal fasciculus (*18*, *20*) that connects the parietal to the frontal lobe (*21*) (Fig. 2, C and D) (figs. S1 and S2). The stimulated region was both distinct and remote from other corticocortical pathways, such as the optic radiations or the parietal-temporal connections.

Our findings demonstrate that the SMG, the cSTG, and a poorly known parietal-frontal pathway, the superior occipitofrontal fasciculus (*18*, *20*), but not the rSTG, are critical to the symmetrical processing of the visual scene in humans (*22*). These results provide evidence relevant to the debate about the lesional correlates of neglect, based until now on the relatively imprecise lesion-overlapping method in stroke patients, and support the proposal that damage to the temporal-parietal junction (*7*, *8*, *23*) and the underlying white matter (*15*) is a crucial antecedent of left neglect. As a consequence, there is no need to postulate a segregation of spatial awareness, specific to humans, in the rostral part of the right STG (*14*).

We observed the maximal deviation upon inactivation of the superior occipitofrontal fasciculus in the depth of the IPL. This result specifies the precise anatomical locus of the parietal-frontal pathway in which neglect

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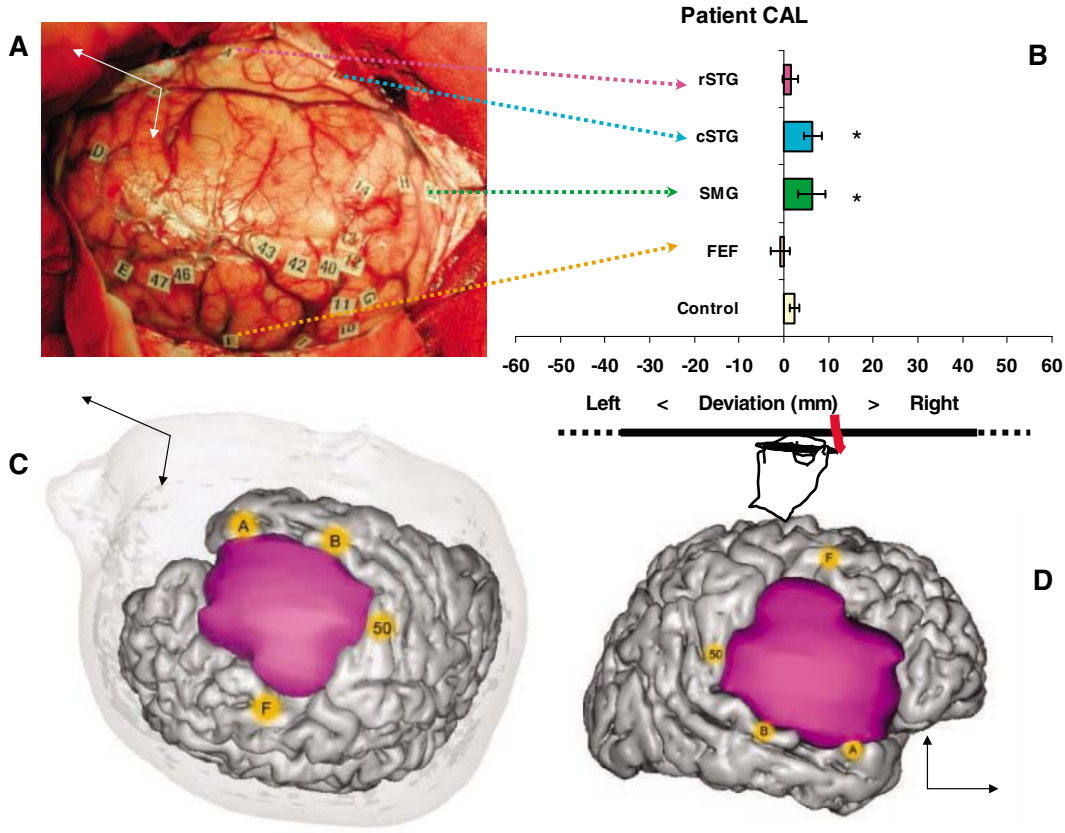

Fig. 1. Performance of patient CAL. (**A**) The surgical field. (**B**) Mean deviation (in millimeters) with 95% confidence intervals during stimulation of the rostral part of the superior temporal gyrus (rSTG, label A; $n = 4$), of the caudal part of the STG (cSTG, label B; $n = 2$), of the supramarginal gyrus (SMG, label 50; $n = 4$), of the frontal eye field (FEF, label F; $n = 5$), and of control neighboring regions (superior frontal gyrus, medial frontal gyrus, precentral gyrus, postcentral gyrus, and tumor, $n = 16$). *$P < 0.05$ (two-tailed) as compared to controls' performance (*32*). (**C**) Three-dimensional reconstruction of the tumor mass (in purple) and of the stimulated regions (in yellow). (**D**) Lateral view.

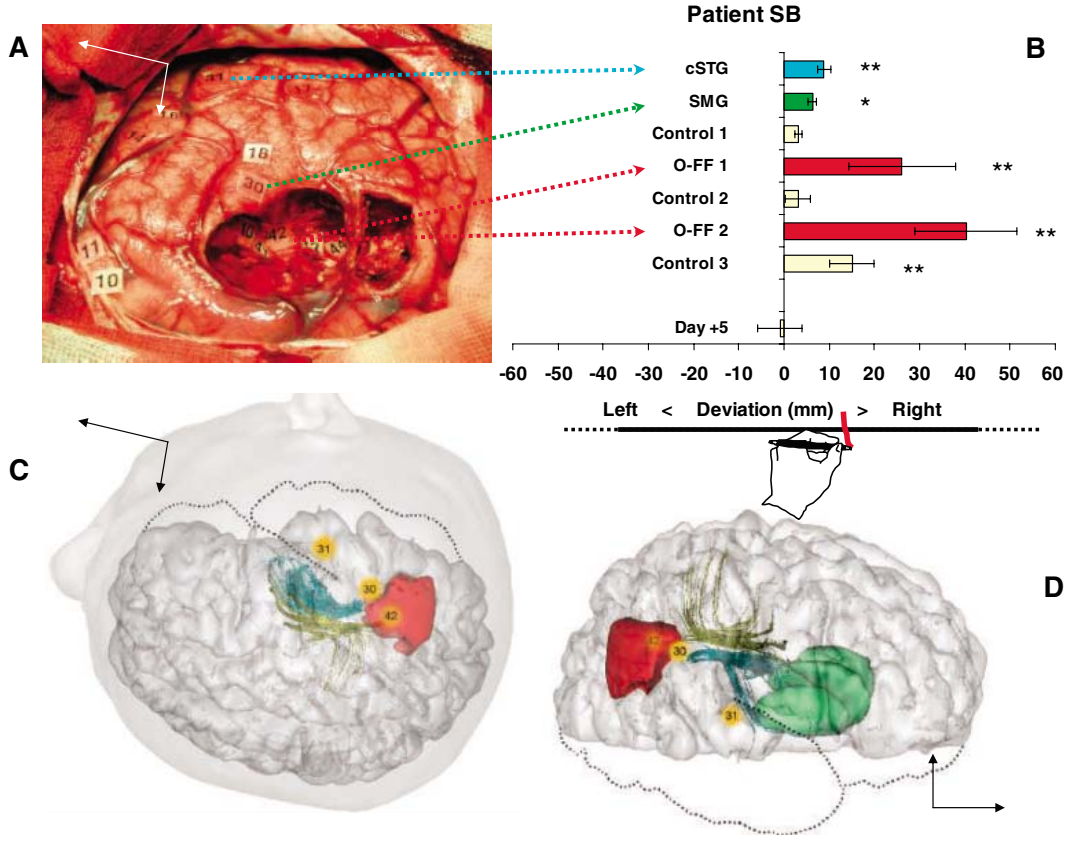

Fig. 2. Performance of patient SB. (**A**) The surgical field. (**B**) Mean deviation (in millimeters) with 95% confidence intervals during stimulation of the caudal part of the STG (cSTG, label 31; $n = 6$), of the supramarginal gyrus (SMG, label 30; $n = 4$), of the superior occipitofrontal fasciculus (label 42) during (O-FF 1; $n = 4$) and after tumor resection (O-FF 2, $n = 4$), and of control neighboring regions (postcentral gyrus, lateral occipital gyri, and tumor) before resection (control 1, $n = 27$), during resection (control 2, $n = 38$), and after resection (control 3, $n = 12$). Performance 5 days after surgery is also shown (day +5). *$P < 0.05$, **$P < 0.01$ (both two-tailed) as compared to controls' performance (*32*). (**C**) Three-dimensional reconstruction of the surgical resection (in red) and of the stimulated regions (in yellow), showing their relationships with the superior occipitofrontal fasciculus (in yellow) and the superior longitudinal fasciculus (in blue) (*18*). The head of the caudate nucleus and the putamen are shown in green. (**D**) Lateral view.

patients' lesions overlap (*15*). Our findings are similar to those obtained in nonhuman primates. Monkeys showed persistent signs of neglect after unilateral section of the white matter between the fundus of the intraparietal sulcus and the lateral ventricle (*24*). The greater effect of subcortical inactivation, as compared to cortical inactivation, is consistent with the idea that symmetrical space processing requires the integrity of a parietal-frontal network (*1*, *15*). Damage to restricted regions of the white matter can cause the dysfunction of large-scale neurocognitive networks. According to an influential model (*1*), signs of left neglect result from impairment of a right-hemisphere network, including prefrontal, parietal, and cingulate components. The parietal component of the network could be especially important for the perceptual salience of extrapersonal objects, whereas the frontal component might be implicated in the production of an appropriate response to behaviorally relevant stimuli (*1*), in the online retention of spatial information (*1*, *25*), or in the focusing of attention on salient items through reciprocal connections to more posterior regions (*20*).

Models of line bisection postulate a competition between the relative salience of the two lateral segments (*6*). The bisection mark is drawn at the point of subjective equality between the two segments (*5*). Bisection-related tasks activate the IPL in humans (*26*). Transcranial magnetic stimulation over the right posterior parietal cortex, but not over the STG, was found to bias the comparison of the lengths of the component segments of pretransected lines in a direction coherent with rightward shifts in line bisection (*27*). In the monkey, regions adjacent to the intraparietal sulcus, such as the lateral intraparietal area, are related to visual perceptual salience (*11*) and can reinforce the stimulus attentional priority (*10*). Parietal inactivation may thus bias the perceptual decision by modulating the salience of the line segments (*6*).

The assessment of spatial cognition during intraoperative stimulation offers the double opportunity of preserving spatial processing functions during brain surgery and of pinpointing the neurocognitive systems devoted to spatial processing in humans. Spatial awareness is dependent not only on the cortical areas of the temporal-parietal junction, but also on a larger parietal-frontal network communicating via the superior occipitofrontal fasciculus.

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17. CAL and SB attended clinical observation because of epileptic seizures. They showed no abnormality on preoperative neurological and neuropsychological examination, consistent with the slowly infiltrative character of low-grade gliomas, whose clinical presentation rarely includes signs of focal brain disease other than epilepsy. In particular, there were no signs of neglect on paper-and-pencil tests (table S1). Intraoperative electrical stimulation was well tolerated, and the patients reported no abnormal visual sensations. They bisected horizontal lines with their left, dominant hand during brain surgery (*28*). Eight healthy left-handed subjects (mean age, 31 years; SD, 5.3; range, 26 to 38) served as controls. They performed 30 line bisections each, with the same test material and in a body position similar to that of the patients. Our patients' baseline performance was well within the range of the controls' performance (mean ± SD, 0.28 ± 2.39 mm) as well as that of 10 strongly left-handed normal individuals tested in another study (*29*) (mean ± SD, –1.50 ± 3.66 mm). In an unselected population of 204 patients with right brain damage (*2*), 5 of the 10 patients with the strongest left-handedness deviated rightward on 20-cm lines as compared to controls (*29*), a frequency of impairment similar to that showed by right-handed patients (*2*).
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19. The neurosurgeon stopped the resection after stimulation of the region labeled as 42 (Fig. 2A). As a consequence, region 42 corresponded to the deepest point on the floor of the rostral-superior part of the surgical cavity, and was thus easily identified on postoperative anatomical MRI scans. The white matter tract underlying region 42 was identified by overlapping the MRI scans with the DTI scans (fig. S1) (Fig. 2, C and D).
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21. The superior occipitofrontal fasciculus is a poorly known long association pathway. It terminates rostrally in the lateral prefrontal cortex of the inferior and middle frontal gyri (*18*). Its caudal terminations are less known (*18*, *30*), but despite its name, derived from early descriptions (*31*), the superior occipitofrontal fasciculus seems to terminate caudally in the superior parietal gyrus (*18*) and in the intraparietal sulcus [(*30*), p. 367].
22. We used line bisection because it is an easy task for patients to perform and allows repeated assessments in the time scale required by intraoperative testing. Bisection of centrally presented 20-cm lines correlates positively and significantly with cancellation tests and is a good predictor of clinical neglect as assessed by standardized scales (*2*, *28*).
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33. We thank the patients for their cooperation; P. Gatignol for help with intraoperative testing; J. Chiras and the Department of Neuroradiology of the Salpêtrière Hospital for MRI acquisitions; S. Kinkingnehun, C. Delmaire, J. B. Pochon, L. Thivard, and the staff of BrainVISA software for technical support for image analysis; and P. Azouvi and the members of the Groupe d'Etude sur la Rééducation et l'Evaluation de la Négligence (GEREN) for permission to use data from GEREN studies (*2*, *29*).

Supporting Online Material

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Breakdown of Cortical Effective Connectivity During Sleep

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When we fall asleep, consciousness fades yet the brain remains active. Why is this so? To investigate whether changes in cortical information transmission play a role, we used transcranial magnetic stimulation together with high-density electroencephalography and asked how the activation of one cortical area (the premotor area) is transmitted to the rest of the brain. During quiet wakefulness, an initial response (~15 milliseconds) at the stimulation site was followed by a sequence of waves that moved to connected cortical areas several centimeters away. During non–rapid eye movement sleep, the initial response was stronger but was rapidly extinguished and did not propagate beyond the stimulation site. Thus, the fading of consciousness during certain stages of sleep may be related to a breakdown in cortical effective connectivity.

When awakened early in the night from non–rapid eye movement (NREM) sleep, people often report little or no conscious experience (*1*). It was first thought that this fading of consciousness was due to the brain shutting down. However, although brain metabolism is re-

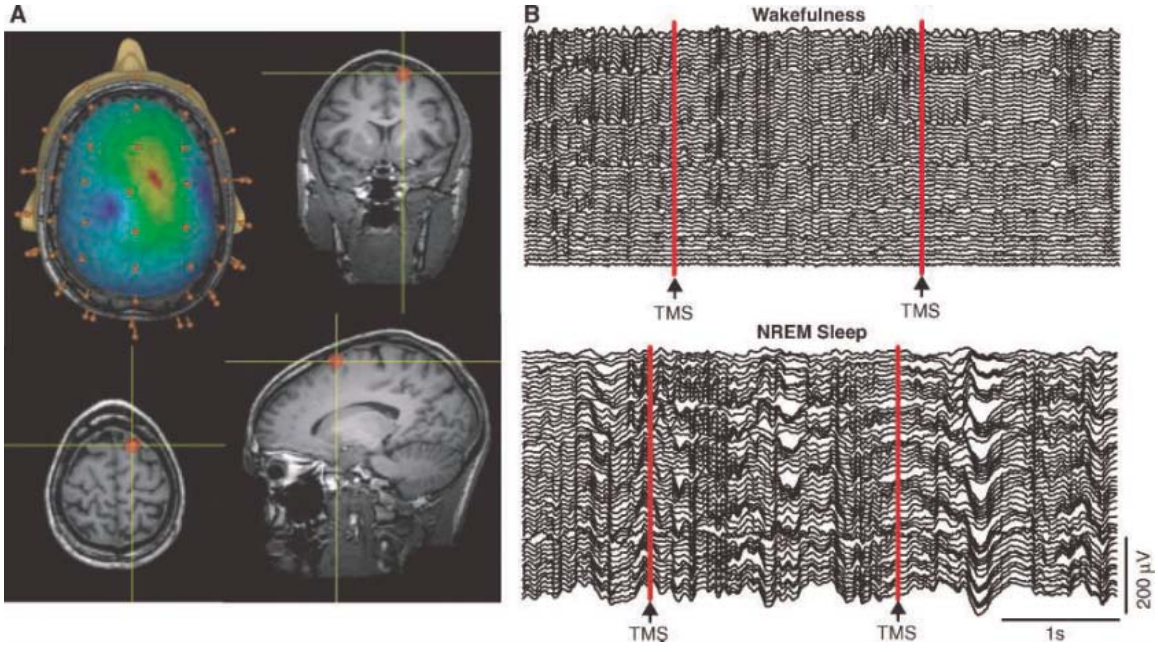

Fig. 1. Navigated brain stimulation and EEG recordings during TMS. (**A**) The estimated electric field induced by TMS on the cortical surface in one subject is color-coded. The red area indicates the location of the maximal electric field strength (in this case, 81 V/m) and corresponds to the coordinates of the rostral premotor cortex, as identified on the three orthogonal projections of the subject's MRI. The brown pins represent the digitized electrodes. (**B**) Multichannel EEG recorded during wakefulness and NREM sleep while TMS (red) was delivered.

duced, the thalamocortical system remains active, with mean firing rates close to those that occur during quiet wakefulness (*2*). Moreover, coherent or synchronized activity continues to be detected among distant cortical areas (*3*–*5*), and sensory signals still reach the cerebral cortex (*6*). Why, then, does consciousness fade?

Recently we have proposed that consciousness depends critically not so much on firing rates, synchronization at specific frequency bands, or sensory input per se, but rather on the brain's ability to integrate information, which is contingent on the effective connectivity among functionally specialized regions of the thalamocortical system (*7*). Effective connectivity refers to the ability of a set of neuronal groups to causally affect the firing of other neuronal groups within a system (*8*). The fading of consciousness during NREM sleep episodes early in the night, evidenced by short or blank reports of cognitive activity upon awakening (*1*), would then be associated with an impairment of cortical effective connectivity.

To test this prediction, we used a combination of navigated transcranial magnetic stimulation (TMS) and high-density electroencephalography (HD-EEG) to measure the brain response to the direct perturbation of a chosen cortical region noninvasively and with good spatiotemporal resolution (*9*, *10*). Using TMS/EEG to investigate critical differences in the functioning of the waking and sleeping brain offers several advantages. Unlike sensory stimulation, direct cortical stimulation does not activate the reticular formation and bypasses the thalamic gate. Thus, it directly probes the ability of cortical areas to interact, unconfounded by peripheral effects. Also, since study subjects reported that they were not aware of the TMS pulse, neural responses are not contaminated by reactions that may result from becoming aware of the stimulation. Most important, the combination of TMS and HD-EEG dissociates effective connectivity (causal interactions) from functional connectivity [temporal correlations (*8*)].

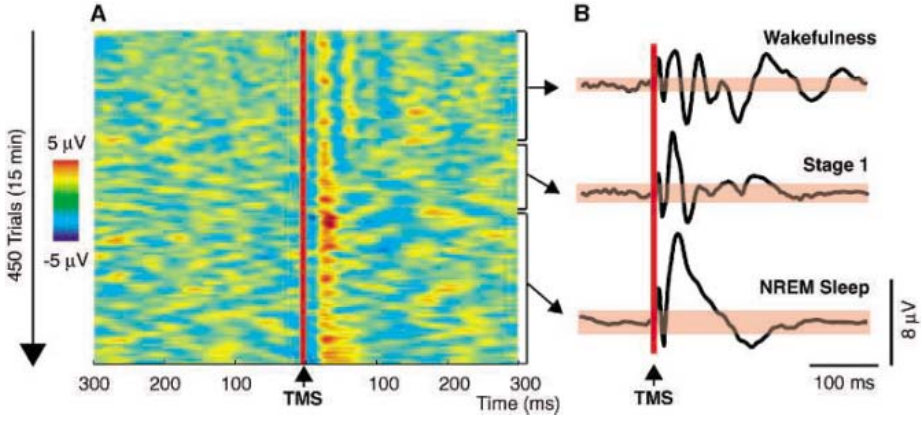

Fig. 2. Changes in the TMS-evoked response during shifts in the state of vigilance. (**A**) Single trials recorded from one channel located under the stimulator while the subject (the same as in Fig. 1) transitioned from wakefulness through stage 1 to NREM sleep. Single-trial EEG data (filtered from 4 to 100 Hz) are color-coded for voltage. (**B**) Averaged TMS-evoked responses (filtered from 1 to 100 Hz) obtained during the three states of vigilance. The horizontal pink bands indicate the significance level (3 SD from the mean prestimulus voltage).

Using a 60-channel TMS-compatible EEG amplifier, we recorded TMS-evoked brain responses while six subjects, lying with eyes closed on a reclining chair, progressed from wakefulness to NREM sleep. By means of magnetic resonance image (MRI)–guided estimation of the electric field induced on the surface of the brain (Fig. 1A), we targeted TMS to the rostral portion of the right premotor cortex. This is an area with extensive corticocortical connections that can be conveniently stimulated without eliciting muscle artifacts. Stimuli were delivered at random intervals (between 2 and 2.3 s) with intensity below the motor threshold (90%), resulting in a maximum electric field at the cortical target of between 75 and 84 V/m. We took special care to reduce the amount of auditory and somatosensory stimulation associated with each TMS pulse (*11*).

As shown in Fig. 1B, TMS did not interfere conspicuously with ongoing wake or sleep EEG patterns nor did it cause visible artifacts. However, TMS elicited a time-locked response that was visible on a single-trial basis

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and that changed markedly from wakefulness to sleep. Figure 2A displays the single-trial responses recorded from one electrode located under the stimulator during a transition from wakefulness through stage 1 to NREM (stages 2 and 3) sleep (in the same subject as in Fig. 1). Figure 2B shows the averages calculated from the single trials collected in these three vigilance states. During wakefulness, TMS induced a sustained response made of recurrent waves of activity. Specifically, a sequence of time-locked high-frequency (20 to 35 Hz) oscillations occurred in the first 100 ms and was followed by a few slower (8 to 12 Hz) components that persisted until 300 ms. As soon as the subjects transitioned into stage 1 sleep, the TMS-evoked response grew stronger at early latencies but became shorter in duration: The amplitude of the initial components increased by 50 to 85% between 0 and 40 ms, whereas the subsequent waves were markedly dampened and fell below prestimulus noise levels (3 SD from the prestimulus baseline mean) within the first 150 to 200 ms. With the onset of NREM sleep, the brain response to TMS changed markedly. The initial wave doubled in amplitude and lasted longer. After this large wave, no further TMS-locked activity could be detected, except for a slight negative rebound between 80 and 140 ms. Specifically, fast waves, still visible during stage 1, were completely obliterated, and all TMS-evoked activity had ceased by 150 ms.

To better characterize the underlying neural events, we calculated the spatiotemporal dynamics of the currents induced by TMS in the cerebral cortex. We digitized and coregistered electrode positions to each subject's MRI, and we constructed a realistic head model. We then estimated current density on the cortical surface by using the weighted minimum norm least-squares method (*11*). Figure 3 shows the average responses recorded from all channels during wakefulness and NREM sleep in the same subject shown in Figs. 1 and 2. At early latencies, during both wakefulness and NREM sleep, TMS induced a clear dipolar voltage configuration that was centered under the coil and corresponded to maximum cortical activation in ipsilateral area 6. During wakefulness, this initial response was followed for about 300 ms by multiple waves of activity associated with rapidly changing configurations of scalp potentials. Current maxima shifted over time from the stimulation target to contralateral area 6, bilateral area 9, contralateral area 8, and ipsilateral area 7. The rostral premotor cortex has extensive transcallosal connections (*12*) and is linked to prefrontal areas (*13*). Thus, during wakefulness, the perturbation of the rostral premotor cortex was followed by spatially and temporally differentiated patterns of activation that appeared to propagate along its anatomical connections. In striking contrast, during NREM sleep the location of maximum current density remained confined to the stimulated area.

As shown in Fig. 4, this breakdown in effective connectivity during sleep was evident and reproducible in all six subjects. We estimated current density whenever the global power of the evoked field was higher (>6 SD) than mean prestimulus levels and plotted the location of the strongest TMS-evoked activation on each subject's cortical surface, color-coded according to its latency (*11*). During wakefulness, the site of maximum activation moved back and forth among premotor and prefrontal areas in both hemispheres and, in some subjects, it also involved the motor and posterior parietal cortex. During NREM sleep, by contrast, the activity evoked by TMS did not propagate in space and time in any of the subjects. In two subjects, we were also able to stimulate the parietal cortex (area 5), and we found a similar impairment of intracortical information transmission during NREM sleep (fig. S2). Thus, although TMS during sleep elicits an initial response that is even stronger than during wakefulness, this response remains localized, does not propagate to connected

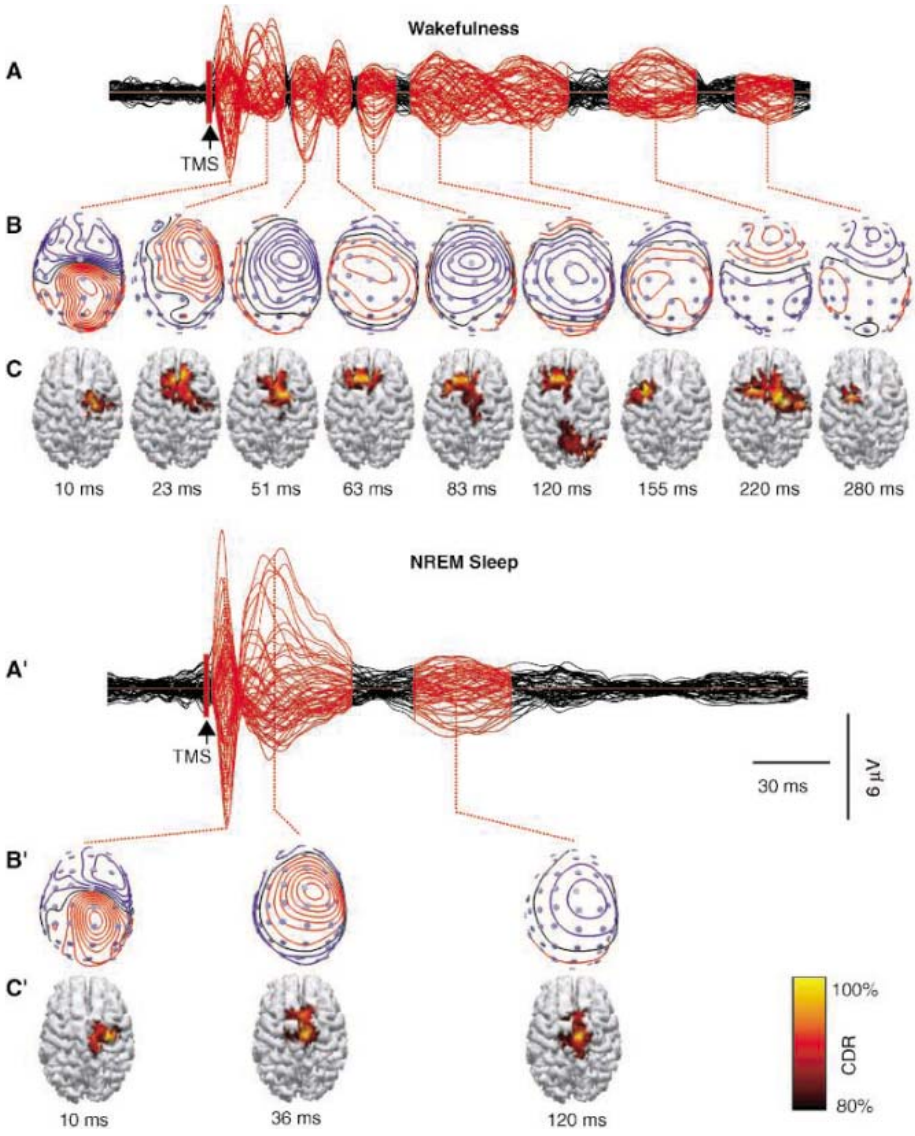

Fig. 3. Spatiotemporal dynamics of scalp voltages and cortical currents evoked by TMS during wakefulness and sleep. (**A** and **A′**) Averaged TMS-evoked potentials recorded at all electrodes, superimposed in a butterfly diagram (black traces; the horizontal red line indicates the average reference), for the same subject as in Figs. 1 and 2. The time of TMS is marked by a vertical red bar. The red portions of the traces indicate the times at which TMS induced a significant response (see supporting online material for calculation details). Source modeling was performed at the local maxima of field power within periods of significant activity. (**B** and **B′**) Three-dimensional contour voltage maps (red, positive; blue, negative; step = 0.6 μV for wakefulness and 1 μV for NREM sleep). (**C** and **C′**) Corresponding current density distributions plotted on the cortical surface. At each time point, the results of the L2 Norm (see methods) were auto-scaled and thresholded at 80% to highlight maximum current sources (CDR, current density reconstruction).

brain regions, dissipates rapidly, lacks high-frequency components, and is stereotypical regardless of stimulation site.

Various mechanisms could account for the enhancement of early TMS-EEG responses in sleep, including a stronger driving force in hyperpolarized postsynaptic neurons (*14*), an increased discharge synchrony of cortical populations (*15*), a reduction in synaptic depression (*16*, *17*), and thalamic bursting triggered by the TMS-induced corticothalamic volley (*18*). These mechanisms may also produce the enhancement of cortical components of visual, auditory, and somatosensory evoked potentials that has been reported during NREM sleep (*6*).

What causes the dramatic breakdown in cortical effective connectivity during sleep? During NREM sleep, cortical neurons are depolarized and fire tonically just as in quiet wakefulness, but these depolarized up-states are interrupted by short hyperpolarized down-states when neurons remain silent (*19*). The transition from up- to down-states appears to be due to depolarization-dependent potassium currents that increase with the amount of prior activation (*19*). Perhaps because of this bistability of cortical networks during NREM sleep (*16*, *17*), any local activation, whether occurring spontaneously or induced by TMS, will eventually trigger a local down-state that prevents further propagation of activity. Alternatively, the block may occur in the thalamus, whose neurons, when hyperpolarized, fire a single burst in response to corticothalamic volleys and then enter a prolonged inhibitory rebound (*20*). Finally, there may be sleep-related changes in the balance between excitation and inhibition (*21*), as suggested by paired-pulse TMS studies (*22*).

Whatever the precise mechanisms, they are most likely engaged by the progressive reduction of the firing of diffuse neuromodulatory systems that occurs when we fall asleep (*23*). Indeed, the blockade of intracortical signaling did not begin suddenly, and the spatiotemporal pattern of cortical activation during stage 1 sleep was intermediate between those of wakefulness and NREM sleep (fig. S3). Specifically, during stage 1 sleep, the TMS-evoked response propagated from the right premotor cortex to the homotopic contralateral site within the first few tens of milliseconds; however, this initial activation was not sustained nor did it reach prefrontal or parietal areas.

By using a combination of TMS and HD-EEG, we have found evidence for a breakdown of transcallosal and long-range effective connectivity during NREM sleep. This breakdown in the ability of cortical areas to interact effectively contrasts with the persistence or increase in interhemispheric and interareal broadband coherence that can be observed in EEG studies of sleep (*3*, *24*). Thus, an impairment in the ability to integrate information among specialized thalamocortical modules—a proposed theoretical requirement for consciousness (*7*)—may underlie the fading of consciousness in NREM sleep early in the night. It will be important to see whether cortical effective connectivity recovers in part during late-night sleep, especially during REM sleep, a time at which conscious reports become long and vivid (*1*). More generally, probing the brain's effective connectivity directly may prove useful in pharmacologically induced unconsciousness and in several psychiatric and neurological conditions in which consciousness is affected and neural interactivity may be compromised above and beyond neural activity and neural synchrony (*25*).

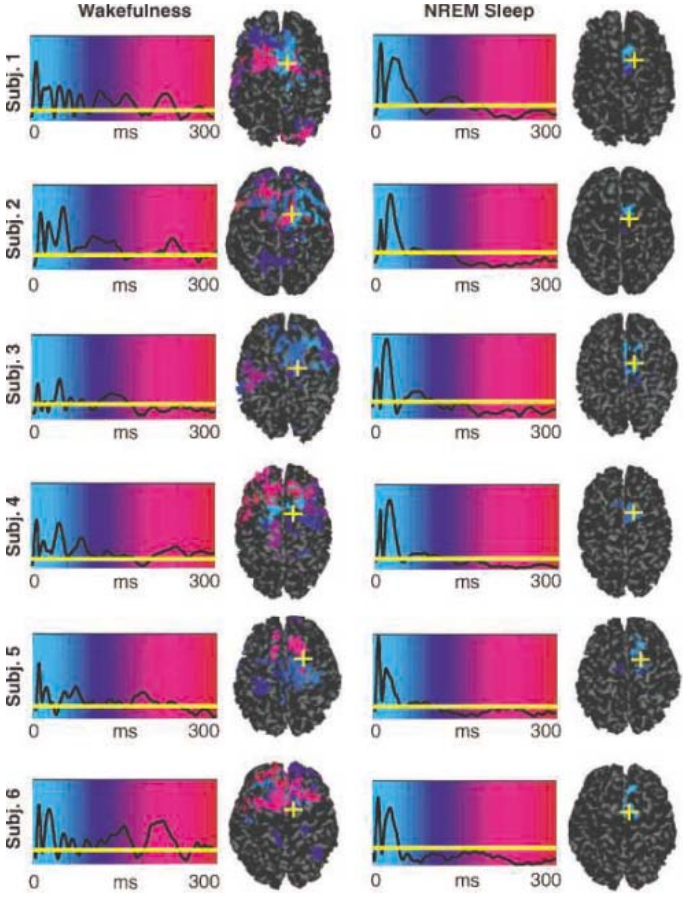

Fig. 4. Spatiotemporal cortical current maps during wakefulness and NREM sleep in all six subjects. Black traces represent the global mean field powers, and the horizontal yellow lines indicate significance levels. For each significant time sample, maximum current sources were plotted and color-coded according to their latency of activation (light blue, 0 ms; red, 300 ms). The yellow cross marks the TMS target on the cortical surface.

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5. Gamma activity and synchrony, which have been viewed as possible correlates of consciousness (*26*–*28*), were found to be low in NREM sleep in one study (*29*). However, they were equally low in REM sleep, when conscious experience is usually vivid, and they can be high during anesthesia (*30*). Moreover, intracellular recordings show that gamma activity persists during NREM sleep (*31*), and other studies report that gamma coherence is a local phenomenon that does not change between wakefulness and sleep (*32*). Large-scale synchrony in the alpha and theta bands may also correlate with conscious perception during wakefulness (*33*), but synchrony in these frequency bands actually increases during NREM sleep (*3*, *34*).
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Supporting Online Material
www.sciencemag.org/cgi/content/full/309/5744/2228/DC1
Materials and Methods
Figs. S1 to S3
References and Notes

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IP_3 Receptor Types 2 and 3 Mediate Exocrine Secretion Underlying Energy Metabolism

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Type 2 and type 3 inositol 1,4,5-trisphosphate receptors (IP_3R2 and IP_3R3) are intracellular calcium-release channels whose physiological roles are unknown. We show exocrine dysfunction in IP_3R2 and IP_3R3 double knock-out mice, which caused difficulties in nutrient digestion. Severely impaired calcium signaling in acinar cells of the salivary glands and the pancreas in the double mutants ascribed the secretion deficits to a lack of intracellular calcium release. Despite a normal caloric intake, the double mutants were hypoglycemic and lean. These results reveal IP_3R2 and IP_3R3 as key molecules in exocrine physiology underlying energy metabolism and animal growth.

Inositol 1,4,5-trisphosphate receptors (IP_3Rs) are intracellular Ca^{2+} release channels located on the endoplasmic reticulum (ER) that mediate Ca^{2+} mobilization from the ER to the cytoplasm in response to the binding of a second messenger, inositol 1,4,5-trisphosphate (IP_3) (*1*). IP_3-induced Ca^{2+} release is triggered by various external stimuli, and most nonexcitable cells use this mechanism as the primary Ca^{2+} signaling pathway. IP_3Rs are therefore thought to have important physiological roles in various cell types and tissues (*2*). Three subtypes of IP_3Rs, derived from three distinct genes, have been identified in mammals (*3*). Type 1 IP_3R (IP_3R1) is predominantly expressed in brain tissue and plays a critical role in the regulation of motor and learning systems (*4–7*). The other two subtypes, type 2 and 3 IP_3Rs (IP_3R2 and IP_3R3), are expressed in various tissues and cell lines (*8–11*); however, the importance of these subtypes in vivo has been difficult to assess because of their coexpression in tissues and the lack of selective inhibitors. In this study, we examined mice lacking both IP_3R2 and IP_3R3 and observed defects in the digestive system resulting from the lack of Ca^{2+} signaling in exocrine tissues. In such exocrine tissues, secretagogue-induced increases in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) trigger the secretion of enzymes or water by acting on the Ca^{2+}-dependent exocytotic machinery or ion channels, respectively (*12–16*). A crucial physiological role of IP_3Rs in exocrine Ca^{2+} signaling was demonstrated (*15*, *17*); however, the relative importance of the three different IP_3R subtypes has been unclear.

We generated mice lacking either IP_3R2 or IP_3R3 by disrupting the corresponding genes within their first coding exons (figs. S1A and S1B). The single-gene mutants were viable and showed no distinct abnormalities in appearance, at least for several months after birth. Mutant mice lacking both of these IP_3R subtypes were also viable during the embryonic period. Immunoblot analysis of the submandibular glands and the pancreas, where IP_3R2 and IP_3R3 are expressed (fig. S1C), showed that expression of IP_3R2 and IP_3R3 was abolished in the mutants (Fig. 1A). At birth, the appearance of double homozygotes was indistinguishable from that of nonhomozygous littermates, but double homozygotes had gained less body weight after birth. After the weaning period, around postnatal day 20 (P20), the homozygotes began losing weight and died within the 4th week of age (Fig. 1B). We suspected that an incapability of the double mutants to eat dry food after weaning might have caused body weight loss and eventual death. Indeed, double mutants did not consume dry food at all. When the double mutants were fed wet mash food beginning at P20, they consumed this type of food and survived thereafter. Body weight increases of the double mutants, however, were still smaller than those of nondouble mutant littermates equally fed with wet mash food (Fig. 1C). Interestingly, despite their reduced body weights, the double mutants consumed no less wet mash food than did the control mice (Fig. 2A and fig. S2A). The double mutants also took as much milk as did control mice when they were fed milk instead of wet mash food after weaning (fig. S2B). Thus, the caloric intake of the $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ double mutants appeared to be slightly greater than that of the control mice. In addition, the amount of feces produced by adult mice fed wet mash food was higher in the double mutants (Fig. 2B). The total amount of proteins and lipids in the feces were higher in the double mutants (Fig. 2C and fig. S2C). Furthermore, blood glucose concentrations were significantly lower in the double mutants (86.1 ± 5.3 mg/dl, $n = 11$) than those in control mice (156.1 ± 6.5 mg/dl, $n = 14$). Altogether, these results suggest that digestive system dysfunction causes the malnutrition phenotype of the double mutants. Actually, when the double mutants were fed a predigested diet containing glucose and amino acids for a week, they gained weight (1.7 ± 0.7 g, $n = 8$), whereas those fed wet mash food did not (–0.5 ± 0.3 g, $n = 5$).

Because the lethal double mutant phenotype was partially rescued by macerating the food with water, we hypothesized that the double mutants might be deficient in saliva production. We therefore examined saliva secretion in adult mice stimulated by subcutaneous

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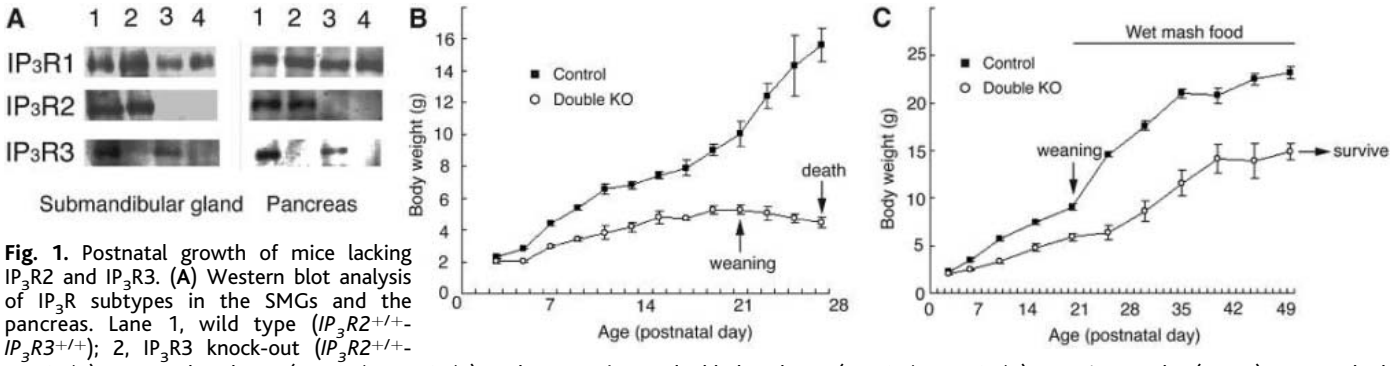

Fig. 1. Postnatal growth of mice lacking IP_3R2 and IP_3R3. (**A**) Western blot analysis of IP_3R subtypes in the SMGs and the pancreas. Lane 1, wild type ($IP_3R2^{+/+}$-$IP_3R3^{+/+}$); 2, IP_3R3 knock-out ($IP_3R2^{+/+}$-$IP_3R3^{-/-}$); 3, IP_3R2 knock-out ($IP_3R2^{-/-}$-$IP_3R3^{+/+}$); and 4, IP_3R2/IP_3R3 double knock-out ($IP_3R2^{-/-}$-$IP_3R3^{-/-}$). Protein samples (50 μg) were probed with subtype-specific antibodies. (B and C) Growth curve of male mice fed (**B**) dry or (**C**) wet mash food. Each point is the average body weight (± SEM) of six animals. Control: nondouble mutants.

(s.c.) injection of pilocarpine and isoproterenol, which mimic cholinergic and β-adrenergic stimulation, respectively. Pilocarpine-stimulated salivation was impaired only in the double knock-outs (Fig. 3A). Mice tested immediately after the weaning period also showed similar defects in salivation as above. Electrolyte concentrations of saliva were also altered in the double mutants (fig. S3A). Immunoblot analysis showed that in the submandibular gland (SMG), the largest salivary gland in the mouse, the expression of aquaporin 5 (AQP5), a water channel responsible for saliva secretion (*18*, *19*), was not altered in the double mutants (fig. S3B). This indicates that the normal water route was intact. Cholinergically induced amylase secretion was also greatly impaired in the double knock-outs [6.4 ± 0.4 units (n = 6), compared with 46.2 ± 3.2 units amylase activity in control animals (n = 6), in the total volume of saliva produced in 30 min after pilocarpine stimulation (10 mg/kg)]. These results demonstrate a deficiency in saliva secretion in the double mutants and suggest that it may lead to starvation. In some cases, however, animals with salivation defects survive with standard dry food pellets by drinking more water (*20*, *21*). Because IP_3R double mutants did not show frequent access to water during eating, a learning impairment may be present in the double mutants that prevents them from adapting to an alteration in feeding behavior.

Because salivation in salivary gland acinar cells is triggered by increased $[Ca^{2+}]_i$ (*14*), we measured the $[Ca^{2+}]_i$ in SMG cells isolated from wild-type, $IP_3R2^{-/-}$, $IP_3R3^{-/-}$, or $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ mice incubated with the Ca^{2+}-sensing dye, fura-2. The effect of carbachol (CCh), a cholinergic stimulant that increases $[Ca^{2+}]_i$, was greatly reduced in $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ SMG cells and was moderately reduced in single knock-out $IP_3R2^{-/-}$ or $IP_3R3^{-/-}$ mice (Fig. 3B and fig. S3, C and D). IP_3 production in response to CCh stimulation and capacitative Ca^{2+} entry were normal, and the Ca^{2+} stores were not emptied in $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ SMG cells (fig. S4).

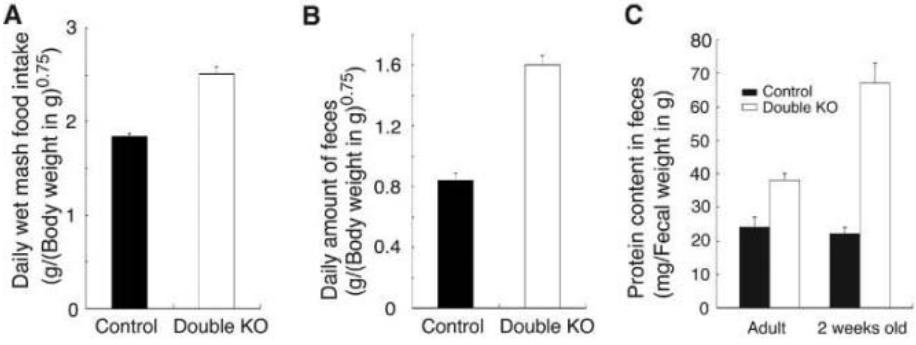

Fig. 2. Feeding behavior and fecal amount of $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ mice. Error bars indicate SEM. (**A**) Wet mash food intake of the double mutant (KO) (n = 4) and the nondouble mutant (control) (n = 6) mice. Food intake was monitored for 10 days beginning at 5 weeks of age and normalized to their (body weights)$^{0.75}$. (**B**) Daily stool mass of adult mice normalized to their (body weights)$^{0.75}$ (n = 12). (**C**) Protein content in the feces of adult (n = 8 per group) and 2 weeks old (n = 7 per group) mice.

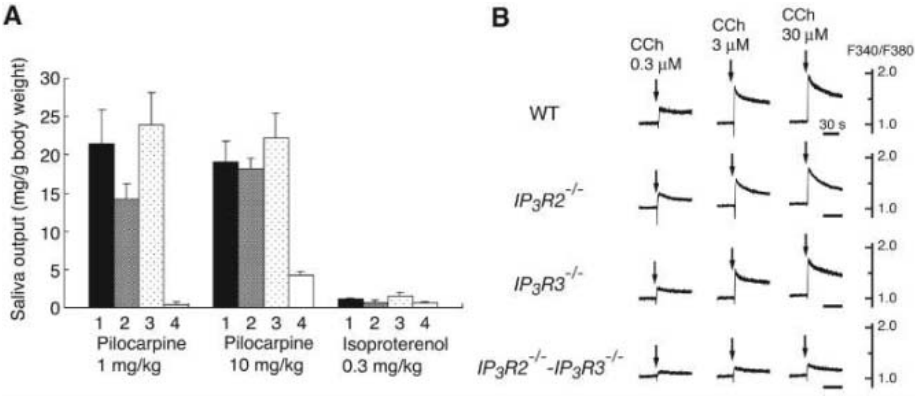

Fig. 3. Saliva secretion and calcium signaling. (**A**) Saliva secretion of adult mice (2 to 3 months old and 4 or 5 mice per group) stimulated by the indicated agonists for 30 min. 1, wild-type; 2, IP_3R2 knock-out; 3, IP_3R3 knock-out; and 4, IP_3R2-IP_3R3 double knock-out. Error bars indicate SEM. (**B**) $[Ca^{2+}]_i$ changes induced by muscarinic receptor stimulation in SMG cells of the indicated genotype. Fura-2-loaded SMG cells were stimulated with CCh at the time point depicted by the arrow.

Histological analysis of the pancreatic tissues, another major exocrine gland, of the double mutants also revealed abnormalities. Pancreatic acinar cells of the $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ double mutants were highly eosinophilic (fig. S5A) and showed abnormal accumulation of zymogen granules (Fig. 4A). These results suggest that unreleased zymogen granules accumulate in the cytoplasm of acinar cells. To evaluate the function of the exocrine pancreas, we stimulated dissociated pancreatic cells with CCh for 30 min and measured the pancreatic amylase secreted. Although muscarinic receptor–mediated amylase secretion from wild-type, $IP_3R2^{-/-}$, and $IP_3R3^{-/-}$ cells was observed, there was

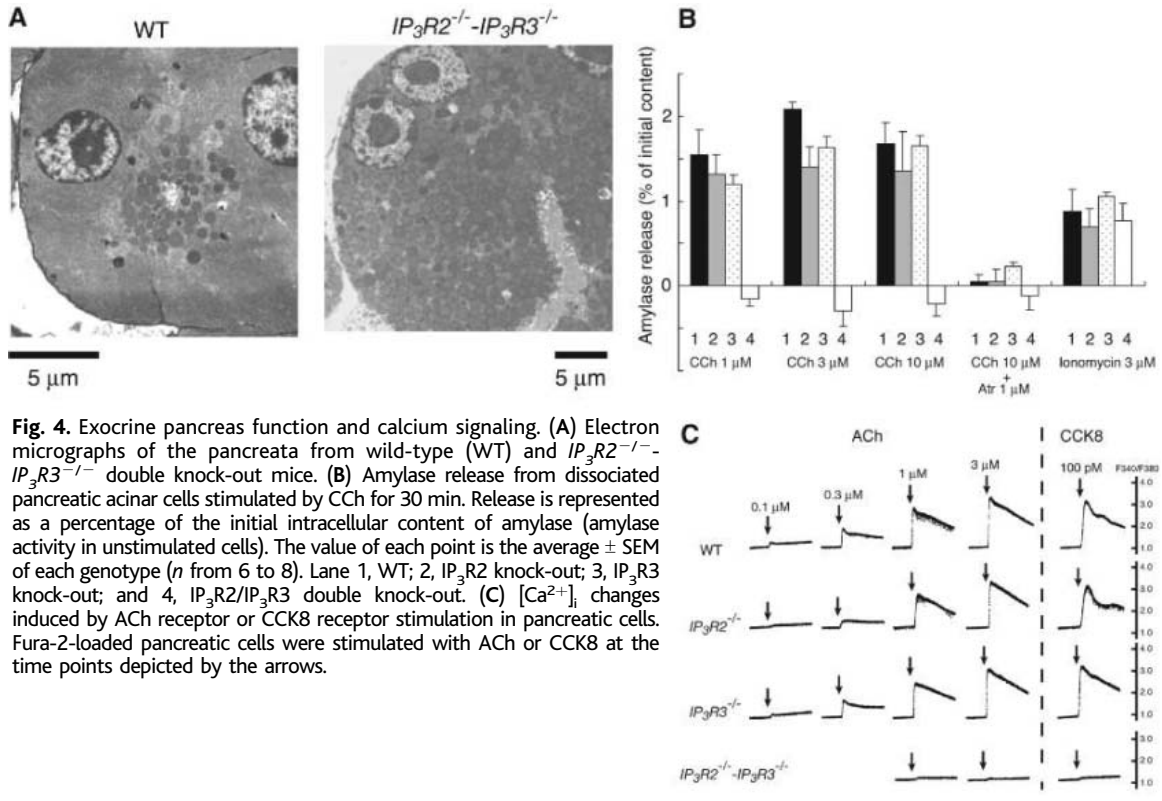

Fig. 4. Exocrine pancreas function and calcium signaling. (**A**) Electron micrographs of the pancreata from wild-type (WT) and $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ double knock-out mice. (**B**) Amylase release from dissociated pancreatic acinar cells stimulated by CCh for 30 min. Release is represented as a percentage of the initial intracellular content of amylase (amylase activity in unstimulated cells). The value of each point is the average ± SEM of each genotype (*n* from 6 to 8). Lane 1, WT; 2, IP_3R2 knock-out; 3, IP_3R3 knock-out; and 4, IP_3R2/IP_3R3 double knock-out. (**C**) $[Ca^{2+}]_i$ changes induced by ACh receptor or CCK8 receptor stimulation in pancreatic cells. Fura-2-loaded pancreatic cells were stimulated with ACh or CCK8 at the time points depicted by the arrows.

almost no CCh-induced amylase secretion from $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ pancreatic cells (Fig. 4B). CCh-induced secretion of lipase and trypsinogen was also abolished exclusively in the double mutants (fig. S5, B and C). Normal amounts of amylase were present in the pancreata of the double mutants (fig. S6A), and ionomycin, a Ca^{2+} ionophore, induced the release of amylase (Fig. 4B). These results indicate that a process mediated by IP_3R2 and IP_3R3 serves as a key step in triggering secretion. This deficiency in exocrine pancreas function may also contribute to the smaller body size of $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ double mutants, which eat no less food than control animals (Fig. 2A). Incomplete digestion of ingested food, resulting from exocrine secretion deficits, would lead to reduced absorption, resulting in an undernourished phenotype.

We examined Ca^{2+} signaling induced by pancreatic exocrine secretagogues in fura-2-loaded, enzymatically dispersed pancreatic cells. No $[Ca^{2+}]_i$ increase was induced by acetylcholine (ACh) or cholecystokinin octapeptide (CCK8) in $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ pancreatic cells (Fig. 4C and fig. S6B and fig. S6C). We confirmed these results with Ca^{2+} measurements in individual acinar cells (fig. S6D). Either IP_3R2 or IP_3R3 could cause Ca^{2+} waves and oscillations initiating at apical poles (fig. S7), consistent with apical localization of these receptors (*22*–*25*). Because the intracellular signal transduction pathway to produce IP_3 was functional and the sarco/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase (ATPase)-sensitive Ca^{2+} stores were not emptied in these cells (fig. S8), we presume that lack of both IP_3R2 and IP_3R3 causes the dysfunction in pancreatic Ca^{2+} signaling. These results demonstrate that IP_3R2 and IP_3R3 are the major Ca^{2+} release channels responsible for secretagogue-induced Ca^{2+} signaling in pancreatic acinar cells and subsequent digestive enzyme secretion. The characteristics of the $IP_3R2^{-/-}$-$IP_3R3^{-/-}$ double mutants represent some symptoms of human diseases. Thus, increasing or decreasing activity of IP_3R2 and IP_3R3 could potentially be of therapeutic benefit.

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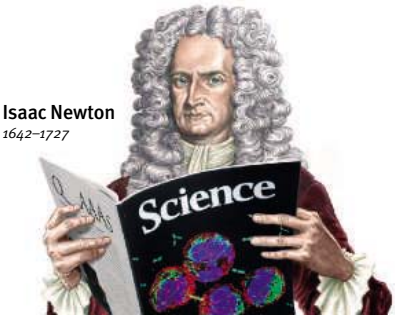

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TOP EMPLOYER

TOP EMPLOYERS SURVEY

Positive Approaches Against Negative Perceptions

Another year, another top employer position for the company that has dominated the rankings in surveys sponsored by *Science's* Office of Publishing and Member Services. But events of the past 12 months have given survey takers an increasingly negative perception of the biopharmaceutical industry.

BY PETER GWYNNE

For the fourth straight year, respondents to the survey to identify top employers sponsored by *Science's* Office of Publishing and Member Services have rated Genentech as the dominant employer in the biotechnology and pharmaceutical industries. But while they show their respect for the northern California company and others that received high ratings, this year's respondents have formed a darker view of the reputation of the biopharmaceutical industry as a whole. Recalls and withdrawals of drugs, and particularly those involving Vioxx, Bextra, and other COX-2 inhibitors, have created a strongly negative image of the industry – an image scarcely mitigated by such positive events as the development of new cancer drugs and approvals of other new medicinal products.

Standing Alone

In terms of perceived quality, Genentech stands alone. Respondents rate the company more highly than others on all the main characteristics that they use to determine their choices of the best employers. Two other firms that do not fill the traditional pharmaceutical mold earn the silver and bronze medals. Amgen, a biotechnology company that, like Genentech, has become a generator and manufacturer of therapeutic drugs, occupies second place in the survey, up from fourth last year. And Johnson & Johnson, a comprehensive health care company that has units devoted to diagnostics and medical devices as well as pharmaceuticals, holds onto the third place that it occupied last year.

Next in line come AstraZeneca and Novartis, each of which has moved up the table from last year's survey. These two Europe-based pharmaceutical firms take a traditional approach to drug discovery, development, and manufacturing but represent newness in that they were created by mergers within the past 10 years. Then, rounding out the top 10 employers, come Genzyme, Eli Lilly and Company, Boehringer Ingelheim, Biogen, and Roche Pharmaceuticals. Boehringer Ingelheim makes its debut in the top 10 this year, while Roche returns to that high standing after a year in which it placed 12th.

The rankings stem from the driving characteristics that respondents to the survey selected as the half dozen factors most critical for a company's success. Those characteristics struck two key themes: an innovative approach to research and a values driven approach to employees.

Just as last year, respondents selected as the most critical driving characteristic the quality of "being an innovative leader in the industry." Related characteristics in third and sixth place were "having a clear vision of where the company is headed" and "doing important quality research." Driving characteristics relevant to employees and their feelings occupy the other three places in the top half dozen. These were: "treats employees with respect," "has work culture values that are aligned to individuals' personal values," and "has loyal employees."

The Element of Respect

Top companies agree with the need to treat their employees respectfully. Richard Scheller, Genentech's head of research, points to the comment of company founder Robert Swanson that "our most valuable asset goes home every night in tennis shoes." CONTINUED »

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"Genentech provides a balance of critical attributes my previous employers were unable to achieve - a strong focus on science, an entrepreneurial spirit, nimble decision-making, a sense of accomplishment and recognition and a place where the employee matters. As a functional area head in Development, I am particularly proud of the excellent staff that we've been able to assemble to focus on the safety evaluation of our new medications. Simply put, Genentech treats its employees extremely well and offers them benefits and career opportunities that few, if any, other biopharmaceutical firms can match."

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"Genentech stands out by successfully executing a very difficult set of strategies, namely selecting to provide medicines to markets of high unmet medical needs in life-threatening diseases and then matching those areas with successful targeted medicines that have their foundation and rationalization in mechanisms of action. As an employer, Genentech creates an environment of scientific excellence and great emphasis on personal contributions towards innovation, while building on personal respect, trust and integrity. Employees are respected by the company, and growth and development are nurtured. Genentech also has a clear vision of its future and clearly communicates that vision to its employees."

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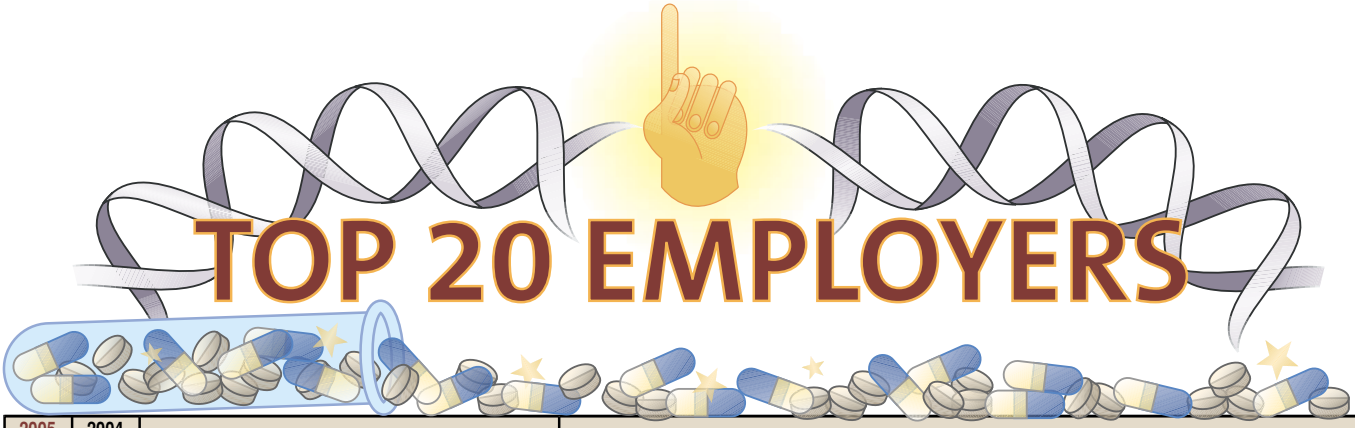

TOP 20 EMPLOYERS

2005 Rank	2004 Rank	Employer (Global Headquarters)	Three Top Characteristics		
1	1	Genentech (South San Francisco, CA)	Innovative leader in the industry	Does important quality research	Clear vision toward future
2	4	Amgen (Thousand Oaks, CA)	Does important quality research	Innovative leader in the industry	Clear vision toward future
3	3	Johnson & Johnson (New Brunswick, NJ)	Treats employees with respect	Does important quality research	Clear vision toward future
4	5	AstraZeneca PLC (London, UK)	Does important quality research	Loyal employees	Treats employees with respect
5	9	Novartis (Basel, Switzerland)	Does important quality research	Innovative leader in the industry	Clear vision toward future
6	6	Genzyme Corporation (Cambridge, MA)	Does important quality research	Innovative leader in the industry	Loyal employees
7	2	Eli Lilly and Company (Indianapolis, IN)	Does important quality research	Loyal employees	Innovative leader in the industry
8	N/A[1]	Boehringer Ingelheim (Ingelheim, Germany)	Does important quality research	Clear vision toward future	Loyal employees
9	10	Biogen Idec (Cambridge, MA)	Does important quality research	Innovative leader in the industry	Treats employees with respect
10	13	Roche (Basel, Switzerland)	Does important quality research	Innovative leader in the industry	Clear vision toward future
11	16	GlaxoSmithKline (London, UK)	Does important quality research	Innovative leader in the industry	Clear vision toward future
12	8	Pfizer, Inc. (New York, NY)	Does important quality research	Innovative leader in the industry	Clear vision toward future
13	12	Monsanto Company (St. Louis, MO)	Does important quality research	Innovative leader in the industry	Clear vision toward future
14	7	Merck & Co., Inc. (Whitehouse Station, NJ)	Does important quality research	Innovative leader in the industry	Loyal employees
15	14	Abbott (Abbott Park, IL)	Clear vision toward future	Does important quality research	Loyal employees
16	11	sanofi-aventis (Paris, France)	Does important quality research	Innovative leader in the industry	Clear vision toward future
17	15	Millennium Pharmaceuticals, Inc. (Cambridge, MA)	Does important quality research	Innovative leader in the industry	Treats employees with respect
18	19	Bristol-Myers Squibb Company (New York, NY)	Does important quality research	Loyal employees	Treats employees with respect
19	18	Wyeth Pharmaceuticals (Collegeville, PA)	Does important quality research	Clear vision toward future	Innovative leader in the industry
20	N/A[1]	Serono (Geneva, Switzerland)	Does important quality research	Clear vision toward future	Loyal employees

The 20 companies with the best reputations as employers, according to respondents from biotech and pharma companies in the survey undertaken for the *Science* Office of Publishing and Member Services.
1. No 2004 rank for Boehringer Ingelheim and Serono due to the fact that neither company received enough mentions during the 2004 survey.

"Genentech is its employees," Scheller adds. "The workers here really feel that is the case from the top right on down." Roger Perlmutter, executive vice president of Amgen, strikes a similar theme. "Having the best team doesn't guarantee that you'll succeed in the drug discovery and development business," he says. "But you can be confident that, if you don't have the best team, you'll fail. We feel that every employee treats every other with trust and respect."

Recognition plays an important role in maintaining scientists' loyalty to their companies. "One very key element is a level of independence afforded to individuals at the same time as a balanced team effort," says Lynne Cannon, vice president and global head of human resources at the Novartis Institutes for BioMedical Research, the Swiss company's research arm. "Our career ladders and recognition system ensure that scientists are recognized for their contributions."

The need to maintain innovative leadership resonates with the nature of the pharmaceutical business during a period when many firms' drug pipelines have started to decline. "The challenge we face in the pharmaceutical industry is not very different CONTINUED »

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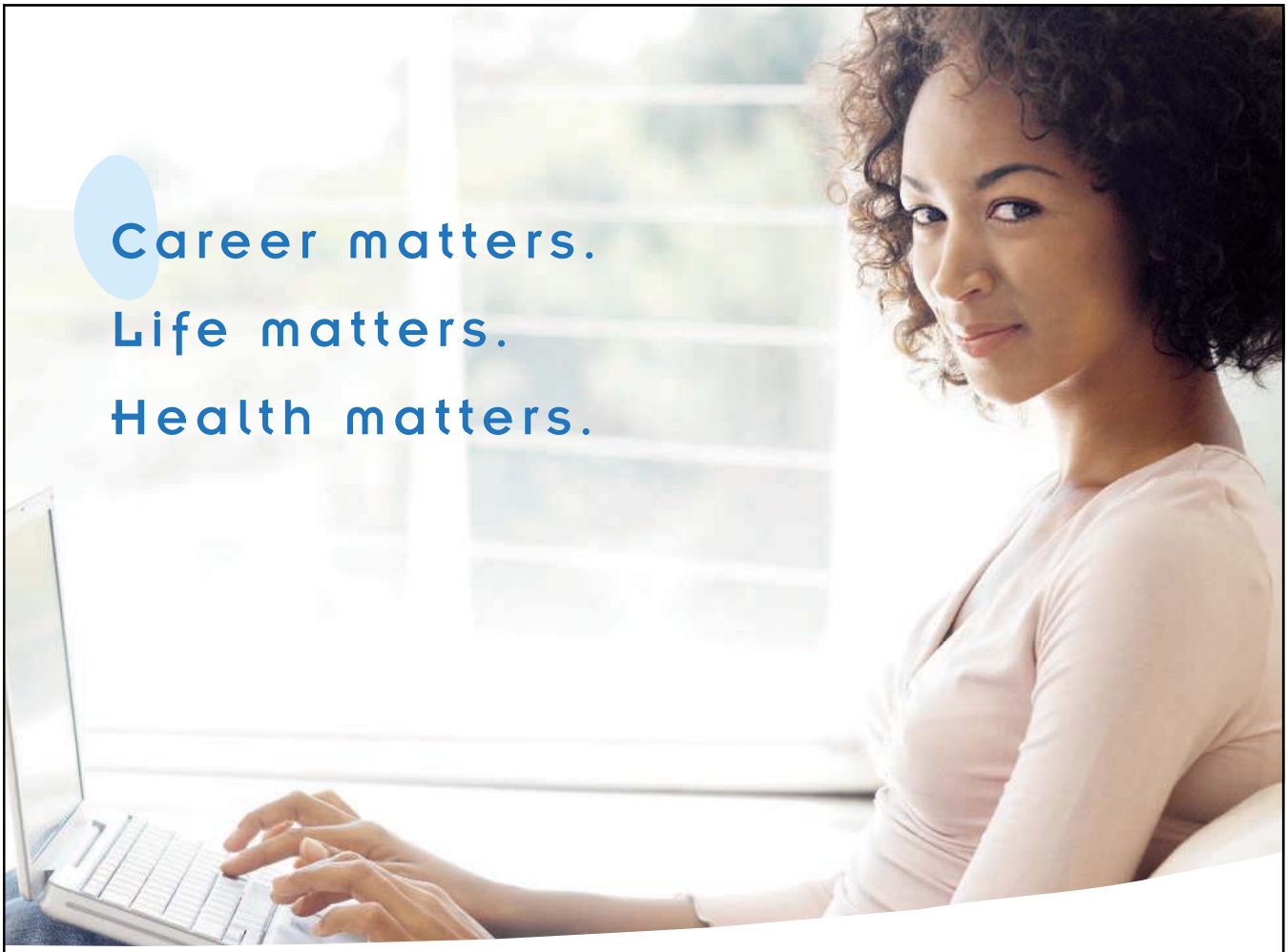

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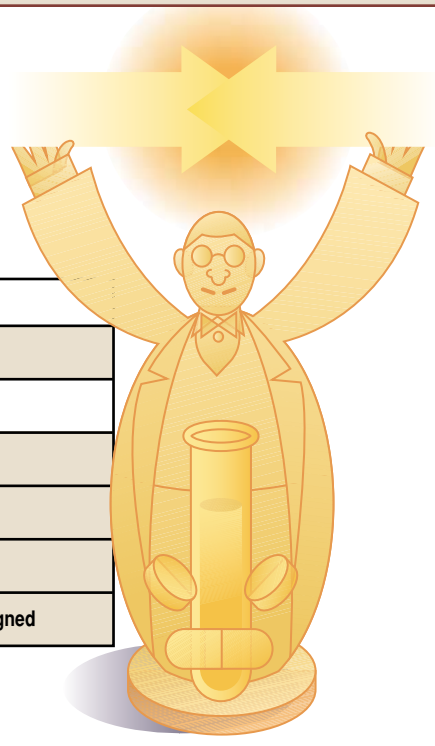
TOP EMPLOYERS SURVEY

Driving Characteristics of Top Employers

2005	2004
1. Innovative leader in the industry	1. Innovative leader in the industry
2. Treats employees with respect	2. Socially responsible
3. Clear vision toward the future	3. Treats employees with respect
4. Work and personal values are aligned	4. Loyal employees
5. Loyal employees	5. Clear vision toward the future
6. Does important quality research	6. Work and personal values are aligned

Colored backgrounds indicate the characteristics in common for the two years.



from that in the movie or music industries: Year after year we have to come out with hits," explains Harlan Weisman, company group chairman, research and development, pharmaceuticals at Johnson & Johnson. "Over the last five to 10 years, just like the movie industry, pharmaceutical companies have come out with product X2, product X3, and other me too drugs. Movies and songs that people like are coming from independents, who are willing to experiment with new ideas and to take risks. We take a similar model that seems to work: We have small units empowered to make decisions from early discovery all the way through to early concept testing in humans. That allows our teams to experiment, create, innovate, follow hunches, and even fail and make mistakes. We want our scientists to learn from their failures."

The Right Resources

That approach relies on the presence of top-notch scientists equipped with the necessary resources. "We maintain quality research by continuing to make investments," declares Lynn Tetrault, human resources vice president for development at AstraZeneca Pharmaceuticals. "We look at external collaborations to bring world class science and new technologies to AstraZeneca. Our scientists see us stretching to bring new things into the company."

Just as important, successful pharmas set out to stretch the inventiveness of their employees by staying away from excessive merger and acquisition activity that has strongly influenced the pharmaceutical industry in recent years. "Boehringer Ingelheim has mainly achieved its growth by innovation through developing its own products or in-licensed products," points out Hans-Joachim Geppert, the company's head of human resources. "Our unique private ownership structure allows for long-term value orientation and strategic persistence." Roche Pharmaceuticals has a different structure but operates in a similar way, according to director of staffing and diversity Brad Smith. "We've avoided the megamergers and other strategies that don't necessarily foster innovation and quality research," he says. "Our goal is to grow organically by investing internally in our in-house research and our relationships with Genentech and other alliance partners."

While they respect individual companies, respondents to the survey looked less favorably on the industry as a whole. "Overwhelmingly, the event that had the greatest impact was a negative," reports Brian Reger of Senn-Delaney Culture Diagnostics & Measurement, who oversaw the survey. Taken collectively, that event involved drug recalls and withdrawals resulting from the prominently publicized failures of drugs that had already reached the marketplace.

Negativity didn't rule the survey entirely. Respondents also noted that the approval and launch of new drugs, and particularly the development of new cancer drugs, gave the pharmaceutical industry a positive image.

Setting Up the Survey

Senn-Delaney conducted the web-based survey between 19 April and 16 May of this year. The firm contacted researchers throughout the world registered with either the American Association for the Advancement of Science (AAAS, publisher of *Science*) or conference organizer IBC Life Sciences who identified themselves as working in biotechnology or pharmaceutical companies. Individual scientists received e-mail invitations from Beth Rosner, publisher of *Science* and director of the AAAS's Office of Publishing and Member Services. The message directed them to a unique, one-person-one-vote URL to ensure that they would vote just a single time. Individuals who did not respond to the initial message received two reminders before the fieldwork ended.

When they logged onto the survey site, respondents first identified the type of organization that employed them. Then they were asked to choose the best, average, and worst employers CONTINUED »

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TOP EMPLOYERS SURVEY

1. Innovative Leader In The Industry

Rank	Employer
1	Genentech
2	Monsanto Company
3	Amgen

2. Treats Employees With Respect

Rank	Employer
1	Genentech
2	Johnson & Johnson
3*	Amgen / Boehringer Ingelheim / Genzyme Corp.

3. Clear Vision Toward The Future

Rank	Employer
1	Genentech
2	Boehringer Ingelheim
3*	Amgen / Monsanto Company

4. Work And Personal Values Are Aligned

Rank	Employer
1	Genentech
2	Boehringer Ingelheim
3	Johnson & Johnson

5. Loyal Employees

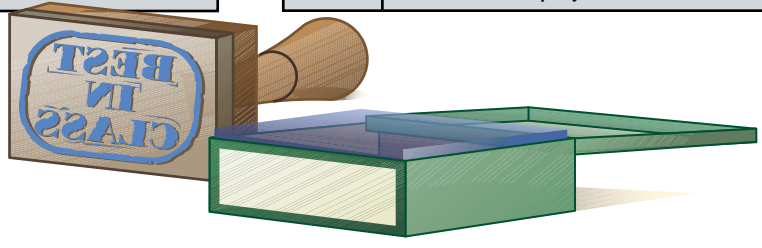
Rank	Employer
1	Genentech
2	Boehringer Ingelheim
3	Eli Lilly and Company

6. Does Important Quality Research

Rank	Employer
1	Genentech
2	Boehringer Ingelheim
3	Monsanto Company

The companies that have the best records on each of the six major driving characteristics, in the view of survey respondents.

* Indicates tie in firms' scores



familiar to them through having worked or consulted for them, collaborated with them, or other means. A total of 37.1 percent of respondents either work currently or used to work for the company they chose as best, while 10.1 percent have or had a consulting or collaborative relationship with that company.

The survey next asked takers to rate the companies they chose on the basis of 42 specific characteristics, such as providing job security, having a research-driven environment, and being socially responsible. Those answers provided the basis of the statistical approach that Senn-Delaney used to determine the top 20 employers. The firm first identified the characteristics that most actively distinguished the best, average, and worst employers selected by respondents. It then applied a statistical process that included frequency analysis, stepwise regression, and discriminant analysis to those characteristics and the companies that possessed them in the views of survey respondents. The result: a unique ranking score for each company mentioned by survey takers.

Statistics of the Sample

The survey also asked respondents for details about their own working and personal demographics. Those questions dealt with such issues as their academic training, the field of their current employment, and the likelihood that they would seek to change jobs within the next 12 months. And a section that encouraged free-form responses asked individuals' opinions on the events of the past year that have had the greatest impact on the biopharmaceutical industry's reputation – for good or ill – and on measures that the industry should take to improve its reputation.

A total of 1,566 individuals completed the survey. Of those, 81 percent work in North America, 14 percent in Europe (including the United Kingdom), and 4 percent in Asia. Slightly less than two-thirds of the sample (64 percent) is male, while about 70 percent are at least 35 years old. Half the survey has at least 10 years of work experience. The sample consists of highly educated scientists; two-thirds have a Ph.D., M.D., or M.D.-Ph.D. degree. Three quarters of respondents CONTINUED »

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declare that they have not yet reached the peak of their careers, and a full 48 percent report that they are "extremely likely," "very likely," or "fairly likely" to look for a different job within the next year.

Respondents work in a wide variety of scientific disciplines, from agricultural sciences to zoology by way of such fields as biotechnology, immunology, medicinal chemistry, and pharmacology. A large majority – 83 percent of the sample – works in private industry. Slightly less than half of the respondents work for biotechnology or biopharmaceutical firms, while pharmaceutical companies employ just under one-third. Companies with at least 5,000 employees account for 46 percent of the sample, and firms with fewer than 1,000 workers 38 percent.

Three Tiers of Achievement

As in previous years, the survey's rankings placed the top 10 employers in three readily identifiable tiers of achievement. But unlike the situation in times past, Genentech occupies the first tier this year in splendid isolation, with a ranking score of more than 90 out of 100. Five companies – Amgen, Johnson & Johnson, AstraZeneca, Novartis, and Genzyme – fill the second tier, which corresponds to scores between 80 and 89. Lilly, Boehringer Ingelheim, Biogen, and Roche make up the third tier, with scores between 70 and 79.

The rankings have a certain familiarity. By earning first place for the fourth year of the four in which *Science* has conducted the survey, Genentech gains the kind of aura enjoyed by such sporting dynasties as the New York Yankees, the Boston Celtics, and the Green Bay Packers of the 1950s and 1960s. Amgen, Johnson & Johnson, AstraZeneca, and Lilly have placed among the top 10 in every year, while Novartis and Genzyme have made the list for the past three years and Biogen for the last two. Of the two new companies that crack this year's top 10, Roche occupied 12th place last year while Boehringer Ingelheim did not feature at all in 2004 because it did not receive enough mentions in that survey.

The six key driving characteristics chosen by this year's survey takers also mirrored last years in several respects. "Being an innovative leader in the industry" emerged as the most important driver, just as it had in 2004. "Treating employees with respect," "having a clear vision of where the company is headed," "having work culture values aligned with individuals' personal values," and "having loyal employees" also made the list this year and last. The only newcomer to the key drivers this year is "doing important quality research."

High Grades on Driving Characteristics

The top employers won the respect of survey takers by scoring high grades on those half dozen driving characteristics. Genentech bested or equaled every other member of the top 10 on each of the six categories. Amgen showed significant advantage over the others on most driving characteristics. And Johnson & Johnson racked up high scores on "treating its employees with respect" and "doing important quality research."

How do top companies maintain their driving characteristics? "We haven't strayed from the mission of translating science into innovative new therapies to improve and save lives," says Genentech's Scheller. "Art Levinson, our CEO, and the executive committee like to think in the long term – where the company will be in 7 to 10 years – and to set very clear goals. Then we aim to explain those goals in a clear and logical way that makes sense to our scientists."

Perlmutter at Amgen makes a similar point. "We focus on human therapeutics," he says. "Our goal is to address grievous illness. We believe that ultimately the best science will win." Weisman of Johnson & Johnson sees the use of various ways to attack medical problems as critical. "Our 'many bets' approach allows us to be at the cutting edge," he explains. "We recognize that there are a lot of great ideas generated outside the company that we can help bring forward for the benefit of patients. We can also combine our expertise, and in fact we are fostering an environment where researchers in our pharmaceutical labs work with those in diagnostics and devices to pioneer treatments that were once unimaginable."

You can find an expanded version of this supplement at http://sciencecareers.sciencemag.org/feature/advice/foc_093005.shl

Companies in the 11th to 20th tranche had similar high grades on the driving characteristics. Monsanto at number 13, for example, scored consistently well on all six characteristics. "We have a vision that the work we do is vital for the health and well-being of others and offers a better quality of life for a global population," explains executive vice president and chief technology officer Robert Fraley. "We maintain those characteristics through our people's commitment to this vision." Abbott meanwhile, in 15th place, scored particularly well on "having a clear vision of where it is headed," and "having loyal employees." "We had a family-friendly workplace ahead of the times," recalls HR group vice president of the global pharmaceutical products group, Jill Mueller. "Our child care center became a wonderful asset for us when the idea of dual working partners became the norm."

Overcoming the Negatives

Executives at top companies also face the task of overcoming the negative views of the biopharmaceutical industry expressed by both the general public and respondents to the survey. "All of us have felt the effects of the recent unfortunate events in the pharmaceutical industry," admits Perlmutter, while pointing out that, as a biotechnology company, Amgen has suffered little direct effect. "We feel it," adds Novartis's Cannon. "But it hasn't affected our recruiting." Other top companies agree that the events have had no impact on their recruitment of first-class scientists.

Boehringer Ingelheim's Geppert argues that such problems are almost inevitable, but that the best companies can reduce the risk. "Product recalls in the light of new information can never be excluded for any company, and the reputation of the pharmaceutical industry has sometimes suffered, even though so much high-class work is being done," he says. "Applicants interested in the pharmaceutical industry are aware of the risk. Therefore it is important to them how reliably a company is focusing its efforts on ethical responsibility to ensure product quality and patient safety." That doesn't imply a continuation of the same old approaches. "We have to adapt to the changing world," says Jenni Hardy, human resources vice president for discovery at AstraZeneca. "We also have belief in our ability to offer different medicines; that continues to attract employees."

Genentech's Scheller summarizes the mixture of distress and hope that the industry faces in the wake of the past year's disturbing news items. "It's a bit painful for medicine that this cloud is over the industry now, as it's the most exciting time the industry has ever experienced," he says. "I'm confident that in the next decade there will be breakthrough therapies the likes of which you have never seen before."

A former science editor of Newsweek, *Peter Gwynne writes about science and technology from his base on Cape Cod, Massachusetts, U.S.A.*

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TOP EMPLOYERS SUPPLEMENT

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–Rosalynn Carter

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VCU
Virginia Commonwealth University

The Department of Anatomy and Neurobiology on the Medical College of Virginia Campus of Virginia Commonwealth University School of Medicine invites applications for two tenure-track positions offered at either the Associate or full Professor level. The Department has 18 full-time Neuroscience faculty whose research is supported by $5 million in extramural funding. Additionally, the Department maintains full-service imaging and molecular biology core facilities. The Department seeks exceptional, established investigators pursuing innovative questions relevant to the Department's research strengths in CNS injury and repair, neural development and plasticity and glial cell biology. Please visit the Departmental website **http://views.vcu.edu/ana** for more detailed information.

Applicants should have a Ph.D., M.D., or D.D.S., with an outstanding research record supported by active extramural funding. Successful candidates will be expected to maintain an externally funded research program and to participate in graduate teaching, as well as pre- and postdoctoral training. The available positions offer attractive salaries that are supported by Institutional funds. In addition, attractive start-up packages and appropriate laboratory space will be provided. Review of applications will begin **October 1, 2005** and the positions will remain open until filled.

Interested candidates should send curriculum vitae, letter of intent including research outline and the name, address, telephone number, fax number and email addresses of three references. Electronic submissions preferred to **anatrecruit@vcu.edu**. Mailing address:

Chair, Faculty Search Committee
Virginia Commonwealth University
Department of Anatomy and Neurobiology
P.O. Box 980709
Richmond, VA 23298-0709

Virginia Commonwealth University is an Equal Opportunity/Affirmative Action Employer. Women, minorities, and persons with disabilities are encouraged to apply.

The CNIC (Spanish National Center for Cardiovascular Research) is a public Foundation funded by the Spanish Ministry of Health and Consumer Affairs through the Carlos III National Institute of Health, and which enjoys substantial investment from the Spanish private sector.

The CNIC offers new opportunities in research and leadership

SIX NEW DEPARTMENT HEAD POSITIONS

The CNIC is an international reference center dedicated to excellence in cardiovascular research and to translating new knowledge into improved medical practice. With the opening of its magnificent new research building in the center of Madrid, the CNIC is entering a new stage in its development. The Center's new building has a total floor space of 23,000 m^2 and is equipped with the latest scientific equipment and research-support technology. When fully occupied this facility will house approximately 300 full-time investigators at different stages of their careers.

As part of its expansion and re-organization program the CNIC is creating 6 separate Research Departments. All Departmental Head positions are now open for recruitment, and the CNIC is therefore seeking leaders in the following areas:

- Vascular Biology and Inflammation (REF: VBI)
- Atherothrombosis and Cardiovascular Imaging (REF: ACI)
- Regenerative Cardiology (REF: RC)
- Cardiovascular Developmental Biology (REF: CDB)
- Cardiovascular Epidemiology and Population Genetics (REF: CEPG)
- Translational Cardiovascular Research of Novel Technologies and Therapeutics (REF: TCRTT)

Applicants must be scientists of international standing with a proven track record of scientific achievement and demonstrated abilities in strategic planning, resource management, and communicative leadership and training.

Successful candidates will benefit from the unique opportunity to enter an expanding and dynamic center at a crucial stage in its development, and will take on the scientific and technical responsibility for providing an excellent research environment for a staff of 40-50 people.

The CNIC offers:

1) salaries competitive with those at other leading biomedical research centers in Europe and the USA

2) significant start-up research support commensurate with experience and track record

3) an attractive benefits package including substantial financial support for national or international relocation

Applications, including a curriculum vitae, publications list, a concise statement of research interests, and the **position reference,** should be submitted by email to

Francisco de Paula Rodríguez Perera, Managing Director
fprodriguez@cnic.es
(Closing date: December 1st, 2005).

The CNIC treats all applicants and employees equally irrespective of nationality, race, ethnic origin, gender, marital or parental status, sexual orientation, creed, disability, age or political belief.

The CNIC is a bilingual institution with Spanish and English as its official languages. All successful candidates must be fluent in at least one of these, and will be expected within a reasonable period after their incorporation to be fluent in both.

Details of our employment policy and further information about the CNIC can be obtained at **http://www.cnic.es**

Positions @ NIH
THE NATIONAL INSTITUTES OF HEALTH

Tenure-Track Investigator Cellular and Molecular Biologist Research Triangle Park, North Carolina

NIEHS National Institute of Environmental Health Sciences

With nation-wide responsibility for improving the health and well being of all Americans, The Department of Health and Human Services oversees the biomedical research programs of the National Institutes of Health.The National Institute of Environmental Health Sciences, a major research component of the National Institutes of Health (NIH) and the Department of Health and Human (HHS) is recruiting a Tenure -Track Investigator-Cellular and Molecular Biologist with research strengths in metabolic nuclear receptors such as peroxisome proliferator-activated receptors (PPARS) and their fundamental mechanisms of action in relation to diseases such as obesity. Research expertise in signaling, transcriptional/translational regulatory mechanisms and molecular imaging is desirable. Model systems need not be restricted to mammals. Applicants should have a Ph.D., MD/Ph.D., MD or equivalent with 3 years of postdoctoral research experience and a strong publication record. The successful applicant will be expected to establish a high-quality independent research program in the area of PPARS or other metabolic nuclear receptors within a basic science research Branch having diverse interests in molecular signaling mechanisms. The applicant will have open access to state-of-the-art equipment and outstanding core facilities (imaging, flowcytometry, microarrays, mass spectrometry, mouse genetics, protein expression, and crystalography). Opportunities exist for interactions with expanding clinical research programs. Excellent laboratory space, start up funds, salary and benefits will be provided. The time before tenure review will be dependent on qualifications but will not exceed 6 years. For additional information about this position, contact **Dr. John A. Cidlowski, Chief, Laboratory of Signal Transduction (cidlows1@niehs.nih.gov).** Highly qualified applicants should send their curriculum vita, with a one page statement of research plan and arrange for three letters of recommendation to be sent to the following address by **December 31, 2005.** Applications received after **December 31, 2005,** will be considered as needed until the position is filled. **Ms. Lisa Rogers (DIR05-11), National Institutes of Health, National Institute of Environmental Health Sciences, P.O. Box 12233, Maildrop A2-06, 111 Alexander Drive, Room A208, Research Triangle Park, NC 27709, e-mail: dir-appls@niehs.nih.gov**

Investigating Transcriptional Responses to the Environment Research Triangle Park, North Carolina

NIEHS National Institute of Environmental Health Sciences

Our laboratory's goal is to elucidate the dynamic interplay between signals from the extracellular environment and chromatin architecture, and to probe how chromatin structure and epigenetics influence gene activity. Although it has been known for many years that the compaction of DNA into chromatin can occlude protein binding sites and gene promoters, the ways in which the cellular machinery manipulates chromatin structure to influence gene expression remain poorly understood. A primary aim of our research is to address two key questions in this field, namely: (i) How do histone modifications and nucleosome remodeling affect Pol II initiation and elongation through a gene? (ii) What are the structural rearrangements that take place in a nucleosome to allow Pol II to access the information within the wrapped DNA?

Understanding the transcriptional response to specific extracellular signals is crucial for a full appreciation of many biological and pathological events involving gene-environment interactions. We are undertaking a broad RNAi screen in Drosophila cell culture to identify proteins that are involved in gene regulation and modifications of chromatin structure during the stress response, accompanied by extensive in vivo and in vitro characterization of the critical factors **(e.g. Adelman, et al., Mol Cell, 2005)**. These studies will take advantage of the availability of cutting-edge Microarray, protein expression, structural biology and Mass Spectrometry facilities at the NIEHS, as well as the novel, single-molecule biophysical techniques that are being developed in our laboratory **(Adelman, et al., Mol Cell, 2004; Adelman, et al., PNAS, 2002)**.

Applicants must possess a Ph.D. in Biochemistry, Biophysics or molecular biology and have less than five years of relevant postdoctoral experience. Salary will be commensurate with experience. Applications should be received no later than **December 7, 2005.** For consideration, send cover letter, curriculum vitae including list of publications, and the names/phone numbers/email addresses of three people who could provide letters of reference to: **Dr. Karen Adelman, Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, Room D454A, Mail Drop D4-02, 111 Alexander Drive, Research Triangle Park, NC 27709, FAX: 919-541-0146, Email: adelmank@niehs.nih.gov, http://dir.niehs.nih.gov/dirlmc/transcript.htm**

Angio/vasculogenesis, Neurogenesis and the Role of Newly Discovered Angiogenic Growth Factors in the Eye

The Unit of Vascular-Retinal Neurobiology Research at the National Eye Institute (NEI) on the main NIH campus in Bethesda, Washington, DC seeks postdoctoral scientists to study the angio/vasculogenesis, neurogenesis and the role of newly discovered angiogenic growth factors (e.g., PDGF-C, PDGF-D and VEGF-B) in the eye. Research interests also include eye stem cells, therapeutic potential of growth factors/antagonists in ocular diseases and the underlying molecular and cellular mechanisms; interactions among retinal cells and surrounding epithelial and vascular-associated cells leading to retinal or choroidal pathology. Related references include Nat Cell Biol 2000; 2(5): 302-309; Nat Cell Biol 2001; 3(5): 515-516; J Clin Invest 2005; 115(1):118-127; and N Engl J Med, 2005, 352(17): 1815-1816. The Unit of Vascular-Retinal Neurobiology Research is located in the newly constructed Porter Neuroscience Research Center on the main NIH campus. This building houses state-of-art biomedical research equipments, and an integrated group of investigators from several NIH institutes, encompassing research interests of angio/vasculogenesis, stem cell biology, basic neurophysiology, developmental neurobiology, neurodegenerative disease, tumor biology, etc, thus providing an unusual innovative scientific environment and opportunities for world-class biomedical research. Candidates must have a Ph.D degree and be highly motivated. Training/experience in cell and molecular biology is required. Background in eye/retinal or choroidal neovascularization and animal experiments is an advantage. Program duration is three years with possibility of extension. Salary is in accordance with NIH standard and commensurate with research experience. For more information about NEI and NIH, please visit the following web pages: http://www.nei.nih.gov/ and http://www.nih.gov/

Interested candidates should send a cover letter describing research experience and interests and curriculum vitae to Dr. Xuri Li at NEI/NIH, Porter Neuroscience Research Center, Building 35, 35 Convent Dr. MSC 3729, Bethesda, Maryland 20892, via email (zcy6205@yahoo.com). Other contact: Mica Gordon, NEI, Office of the Scientific Director, gordonmi@mail.nih.gov, 301-451-6763.

Deputy Director Division of Intramural Research National Eye Institute

The Division of Intramural Research, NEI, is searching for a Deputy Scientific Director to work with the Scientific Director in leading and managing the NEI intramural research program and in monitoring, coordinating, and evaluating all aspects of the program's progress in achieving its goals and objectives. The mission of the DIR is twofold: (1) to advance knowledge of how the visual system functions in health and disease using a combination of basic, translational, and clinical science; (2) to develop effective means of prevention, treatment, and rehabilitation for diseases of the eye and visual system. The DIR consists of 32 Principal Investigators and more than 250 scientific support personnel. The laboratory and clinical scientists carry out interdisciplinary studies in genetics, cell and developmental biology, immunology, systems neuroscience, and conduct phase I, II and III clinical trials. In-house core support services include histology, imaging, and knock out and transgenic rodent facilities, and an extensive veterinary research and resources unit.

Applicants for this position must have significant research and administrative experience, an M.D., Ph.D., or equivalent degree in the biomedical sciences, and experience and understanding of administrative policies, procedures, operations, and technology development in a large biomedical research institution. The incumbent's primary responsibilities would be administrative but the possibility exists for some limited individual research activity. The applicant must be a highly collaborative person able to work with diverse groups of individuals, in and out of NIH/NEI. He or she should have skills in science leadership and communication and be innovative in maximizing the impact of available resources. Applicants should submit a curriculum vitae and bibliography to the following address: **Sheila Ayala, Staff Assistant, Office of the Scientific Director, National Eye Institute, Building 31, Room 6A22, 31 Center Drive, Bethesda, MD 20892, Tel: 301-451-6763, EM: sayala@nih.gov**

WWW.NIH.GOV

NIDDK

TENURE-TRACK POSITION IN THE LABORATORY OF CHEMICAL PHYSICS

A tenure track position is available for an experimental biophysical scientist to establish an independent research program in the Laboratory of Chemical Physics, NIDDK, NIH. All areas of biophysics and biophysical chemistry will be considered for this position. Current research in this Laboratory is primarily concerned with experimental, theoretical and computational problems in the structure, dynamics, and function of biological macromolecules, using techniques that include solution and solid-state nuclear magnetic resonance spectroscopy, Raman and infrared imaging spectroscopies, time-resolved X-ray crystallography and optical spectroscopy, and single molecule spectroscopy. The theoretical and computational studies closely complement the experimental work. Development of fundamental aspects of experimental and theoretical techniques is an active area in the Laboratory.

The Laboratory is located on the main intramural campus of the NIH in Bethesda, Maryland, just outside Washington, D.C. The Senior Scientists in the Laboratory are: Philip Anfinrud, Ad Bax, Marius Clore, William Eaton, William Hagins, Gerhard Hummer, James Hofrichter, Ira Levin, Attila Szabo, and Robert Tycko (Scientists Emeritus: Edwin Becker and Robert Zwanzig).

Interested applicants should send a Curriculum Vitae and list of publications, copies of selected publications, a summary of research accomplishments, a plan for future research, and three letters of reference to: **Dr. Sriram Subramaniam, Chair, Laboratory of Chemical Physics Search Committee, Building 5, Room 116, National Institutes of Health, Bethesda, MD 20892-0520.** Deadline for receipt of applications is **December 1, 2005**. Salary and benefits are commensurate with the experience of the applicant.

NIDDK

TENURE-TRACK POSITION IN THE LABORATORY OF CHEMICAL PHYSICS

A tenure track position is available for a theoretical/computational biophysical scientist to establish an independent research program in the Laboratory of Chemical Physics, NIDDK, NIH. Current research in this Laboratory is primarily concerned with experimental, theoretical and computational problems in the structure, dynamics, and function of biological macromolecules. Experimental techniques include solution and solid-state nuclear magnetic resonance spectroscopy, Raman and infrared imaging spectroscopies, time-resolved X-ray crystallography and optical spectroscopy, and single molecule spectroscopy. Development of fundamental aspects of experimental and theoretical techniques is an active area in the Laboratory.

The Laboratory is located on the main intramural campus of the NIH in Bethesda, Maryland, just outside Washington, D.C. The Senior Scientists in the Laboratory are: Philip Anfinrud, Ad Bax, Marius Clore, William Eaton, William Hagins, Gerhard Hummer, James Hofrichter, Ira Levin, Attila Szabo, and Robert Tycko (Scientists Emeritus: Edwin Becker and Robert Zwanzig).

Interested applicants should send a Curriculum Vitae and list of publications, copies of selected publications, a summary of research accomplishments, a plan for future research, and three letters of reference to: **Dr. Richard Pastor, Chair, Laboratory of Chemical Physics Search Committee, Building 5, Room 116, National Institutes of Health, Bethesda, MD 20892-0520.** Deadline for receipt of applications is **December 1, 2005.** Salary and benefits are commensurate with the experience of the applicant.

NIDDK

TENURE-TRACK POSITION IN DEVELOPMENTAL BIOLOGY LABORATORY OF CELLULAR AND DEVELOPMENTAL BIOLOGY

We seek an outstanding scientist to direct a vigorous, innovative research program in molecular mechanisms of development. Applicants must be highly motivated and have a demonstrated track record through publications that address significant biological problems. The successful candidate is expected to develop an independent, world-class research program complementary to current investigations within the Laboratory. The position comes with generous start up funds and on-going support (including salaries for research group) will be provided from intramural research funds.

The Laboratory of Cellular and Developmental Biology, NIDDK is located on the main NIH campus in Bethesda, Maryland, a suburb of Washington, DC. The Laboratory represents interests similar in range to those of an academic department. There are strong interactions among the independent research groups, and the position offers unparalleled opportunities for interdisciplinary collaboration within NIDDK and throughout NIH. Salary and benefits are commensurate with the experience of the applicant. Interested applicants should submit a curriculum vitae, bibliography, copies of three major publications, a summary of research accomplishments, a brief statement of future research goals, and arrange for three letters of reference to be sent to:

Lanette West-Johnson, Office Manager
Laboratory of Cellular and Developmental Biology, NIDDK
50 South Drive, MSC 8028, Building 50, Room 3133
National Institutes of Health, Bethesda, MD 20092-8028

Website: **http://www.niddk.nih.gov/intram/branchlb/lcdb.htm**
Application dateline: **October 28, 2005**

Postdoctoral Research
Biology of RNA Metabolism in Eukaryotes
National Institute of Child Health and Human Development

The successful candidate will investigate molecular mechanisms involved in the metabolism of noncoding and coding RNAs. This includes the link between transcription termination and RNA processing as well as nuclear transport. A major focus is on the conserved La antigen. Fission yeast, mammalian cell culture, and genetically altered mice are studied.

Candidates must hold a Ph.D. and have less than 5 years postdoctoral experience. Expertise in molecular biology, genetics, and/or biochemistry is preferred. Experience in RNA metabolism is desirable. The successful candidate must incorporate self-directed research, excellent technical, presentation, and communication skills as essential parts of the job. Applicants should submit a cover letter that details their specific interest in the research areas described above.

Richard J. Maraia, M.D.
Email: maraiar@mail.nih.gov
URL: http://eclipse.nichd.nih.gov/nichd/Maraia/Maraialabpage.html

Department of Health and Human Services (DHHS)
National Institutes of Health (NIH)
National Cancer Institute (NCI)
Coordinating Center for Clinical Trials

Announcement Numbers: NCI-05-95178
Position: Director, Coordinating Center for Clinical Trials

We are searching for an M.D. and/or Ph.D. physician/scientist of national stature to serve as the Director of the Coordinating Center for Clinical Trials (CCCT), with overall responsibility for implementing, managing, and evaluating all functions of the CCCT. The Director will serve as an authoritative source of scientific expertise on the development and administration of a national clinical trials enterprise, to include solutions to a myriad of regulatory issues. The CCCT has been charged with implementing the recommendations of the National Cancer Advisory Board's chartered Clinical Trials Working Group (CTWG) on the development, conduct, infrastructure, and support necessary for the optimal coordination and future progress of the entire range of intramural and extramural clinical research trials supported by the NCI, including diagnosis, treatment, and prevention studies.

The CCCT will implement four critical initiatives in order to design a restructured national clinical trials enterprise that is not only more efficient and coordinated but founded on the best science. The first initiative is to improve coordination and cooperation among the functionally diverse components of the current system, including industry and Federal regulatory agencies. The second initiative is to improve prioritization and scientific quality by developing an open and transparent process for the design and prioritization of clinical trials that are science-driven and meet the needs of patient care. Additional initiatives that the CCCT will implement include improving standardization of tools and procedures for trial design, data capture, data sharing, and administrative functions to minimize duplication of effort, and to facilitate development of a shared infrastructure to support an integrated national cancer clinical trials network. Another major initiative includes improving operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost-effective manner. More information regarding these initiatives can be found in the final report of the CTWG at: **http://integratedtrials.nci.nih.gov/ict/.**

Total annual compensation will be commensurate with education and experience. Various incentives may apply in individual circumstances based on experience and expertise to increase total compensation to $200,000. A recruitment incentive and relocation expenses may also be available to the selectee. Full Federal benefits including health and life insurance options, retirement, paid holidays, vacation and sick leave will be provided.

To obtain the application requirements and other necessary information, please visit: **http://jobsearch.usajobs.opm.gov/a9nih.asp and search for Vacancy Announcement (VA) NCI-05-95178**. For more information regarding application procedures, please contact **Ms. Mary Lou Weathers at (301) 402-5059.**

Please send, at a minimum, your C.V., Bibliography and Response to the Selective Factor to:

Ms. Mary Lou Weathers
Human Resources Specialist
NIH, OHR, CSD, NCI HR Operations Branch
6120 Executive Boulevard, Room 550
Rockville, MD 20892

Responses to the selection criteria are encouraged. **Application materials may also be faxed to (301) 402-9333 or emailed to weatherm@mail.nih.gov.**

APPLICATIONS MUST BE RECEIVED BY NOVEMBER 14, 2005

THE NEW LIFE SCIENCES INITIATIVE
at Cornell University

CORNELL UNIVERSITY IS CONTINUING ITS $650-MILLION initiative to recruit faculty and provide resources that foster the multidisciplinary study of organisms in the post-genomics era. This faculty-driven effort is integrating the life sciences with Cornell's outstanding programs in the physical, engineering, and computational sciences through 13 interconnected, campus-wide focus areas composing The New Life Sciences Initiative. Beginning in 1998 and extending through these next five years, Cornell is making 120 professorial appointments, with 50 new hires to date, expanding the graduate fellowship program, creating new research core facilities, and constructing the new Life Sciences Technology Building and the East Campus Research Facility (see images on next pages) which together will add 350,000 GSF to research facilities for life scientists. In addition, a new 196,000-GSF Physical Sciences Building, which will have significant life-science emphasis, will be occupied in 2010. There is also strong and increasing support for collaborations between the Ithaca campus and the Weill Cornell Medical College in New York City and with Rockefeller University and Memorial Sloan-Kettering Cancer Center. Active faculty searches are listed on the next three pages. For more information, please visit our websites: `http://vivo.library.cornell.edu`, `http://www.genomics.cornell.edu/`, and `http://lifesciences.cornell.edu/about/initiative.php`.

The main campus of Cornell University, which overlooks 40-mile-long Cayuga Lake, is located in the Finger Lakes region of Upstate New York, a scenic environment of spectacular lakes, waterfalls, gorges, rolling hills, farmland, vineyards, and state parks. It is an area with outstanding recreational and summer and winter sports opportunities for individuals and families. The Cornell campus itself is one of the most beautiful in the country. As a private endowed university that includes several state-assisted colleges and is the state's federal land-grant institution, Cornell comprises an unusually varied array of academic units. It is also a member of the Ivy League. The Ithaca community is culturally diverse with excellent theater, music, sports, and other activities befitting a major university town yet also has the warmth and friendliness of a small community. The area is known for its many bookstores and restaurants, an extensive walking trail system, arboretum, Laboratory of Ornithology, marina, Farmers' Market, a hands-on Sciencenter, and art and science museums. For more information and links to individual attractions, visit `http://www.visitithaca.com/`.

Cornell Institute of Molecular and Cell Biology

Cornell University is creating a new Institute of Molecular and Cell Biology (CIMCB) that has as its goal the investigation of fundamental biological processes that lie at the center of life and cellular function. The new institute will serve as a focal point for research efforts being pursued in life science departments across campus, ranging from genetics and neurobiology to plant science, animal science, and veterinary medicine. A key aspect of CIMCB will be strong interdisciplinary interactions among faculty from different departments. The CIMCB will focus on three key biological processes that occur in a regulatory succession: (1) cellular signaling, (2) the interpretation of these signals at the level of gene regulation and expression, and (3) the execution of this regulation through changes in cellular structure, dynamics, and function.

Schwartz Center for the Performing Arts

While having basic mechanisms of biological function at its core, the intention is that CIMCB will also promote the development of new imaging and other methods to track and manipulate molecules in vitro and in living cells, as well as new genetic- and drug-based methods to selectively inactivate or activate particular molecules in specific cells at designated times. The CIMCB will be housed in the new, Richard Meier–designed Life Science Technology Building (to be occupied in 2007; see image on next page) where the core institute faculty will be complemented by, and in immediate juxtaposition to, faculty who are developing biophysical, chemical, computational, and engineering approaches that can be brought to bear on high-impact questions in basic biology. Cornell is presently searching for a director. Applications for senior and junior faculty positions in the new institute will be solicited in the near future.

Cell Biology

The Department of Molecular Biology and Genetics seeks a tenure-track Assistant Professor of Cell Biology studying the functional organization of cells or tissues. Applicants researching focused genomic approaches to questions in cell biology are especially encouraged to apply. See details in *Science* ad of August 26. The position is part of a campus-wide expansion in cell biology, which includes a new Institute of Molecular and Cell Biology (see above). The successful candidate will be expected to establish a vigorous independent research program and participate in the teaching of cell biology. The department includes faculty with research programs in cell biology, developmental biology, genetics, molecular biology, comparative and population genomics, structural biology, and biochemistry (`http://www.mbg.cornell.edu`). TO APPLY: Candidates should submit a *curriculum vitae*, a description of research plans and teaching interests, plus copies of two papers, as a single PDF file (max. 5MB) to Tony Bretscher, c/o `RLL2@cornell.edu` and arrange for three letters of recommendation to be sent electronically to `RLL2@cornell.edu` and in hard copy to: Tony Bretscher, Cell Biology Search Committee, 107 Biotechnology Bldg., Cornell University, Ithaca, NY 14853. The committee will begin reviewing applications on October 15, 2005.

Bioengineering and Biomedical Engineering

Biomedical Engineering

Cornell seeks faculty working at the interface of engineering and life science that thrive on interdisciplinary research and teaching. Cornell has formed a new Department of Biomedical Engineering (BME) that seeks to bridge medicine, biology, and engineering. The department is guided by a vision of developing a quantitative understanding of the human body across scales as basis for the rational design of devices, diagnostics, and therapies to improve human health. BME is responsible for granting MS/PhD and MEng degrees and sponsors an undergraduate minor in BME available to all students majoring in engineering. Two tenure-track faculty positions in Biomedical Engineering are available with rank open. Research in any area of biomedical engineering will be considered, although there are particular needs for faculty with interests in cellular/tissue bioengineering, molecular/cellular imaging technology, biomaterials, systems biology, and applications of micro/nanofabrication in medicine. Cornell's Center

ScienceCareers.org

for Materials Research, Nanobiotechnology Center, Center for Nanofabrication, Developmental Resource for Biophysical Imaging and Opto-Electronics, and Theory Center provide outstanding facilities to support interdisciplinary research relevant to biomedical engineering. Candidates should have a PhD in Biomedical Engineering or related technical field. TO APPLY: Interested candidates should send a letter of interest, *curriculum vitae*, brief statement of research and teaching interests, list of recent externally supported research, and names of three references to: Bmep_search-mailbox@cornell.edu.

Computational and Statistical Genomics; Evolutionary Genomics

Biological Statistics and Computational Biology

Biological Statistics and Computational Biology is a rapidly expanding, interdisciplinary department focused on the development and application of statistical theory to problems in modern biology. Expertise in the department spans Bayesian and computationally intensive statistics; experimental design; QTL and association mapping; microarray analysis; population and evolutionary genomics; phylogenomics and bioinformatics; and survival analysis. The faculty having thriving


Life Science Technology Building (opens 2007)

collaborations with colleagues in Mathematics, Computer Science, Veterinary Medicine, and Molecular Biology and Genetics play a key role in the Graduate Field of Computational Biology and in the New Life Sciences Initiative. We are currently searching to fill a position at open rank in the area of statistical, evolutionary, and computational genomics. Requirements include a PhD in genetics, molecular biology, biochemistry, biostatistics, computer science, mathematics, statistics, or related area with demonstrated research accomplishments in genomics. TO APPLY: Applicants should send, as a single PDF document, a cover letter, a *curriculum vitae*, a concise statement of research and teaching interests, copies of relevant publications, and the names of at least three references to: culifesciences@cornell.edu. Review of applications will begin November 1, 2005 and continue until the position is filled.

Computational Biology and Bioinformatics

The Department of Computer Science is seeking applicants at all ranks for interdisciplinary tenure-track positions in computational biology. Applicants should have a very strong background in computer science and should also have a strong background and research interest in computational aspects of biology. Research may include such topics as development of genomic databases, bioinformatics, biological networks, and structural biology. We are looking for candidates with outstanding research promise who are committed to excellence in teaching computer science. The department is administered by the Office of Computing and Information Science (CIS), a larger unit that can co-sponsor faculty positions in the Faculty of Computing and Information Science with any department on campus. Further information about the department and the Office of Computing and Information Science is available at http://www.cs.cornell.edu and http://www.cis.cornell.edu/. TO APPLY: Applicants should submit a *curriculum vitae* and the names of at least three references to: Chair, Faculty Recruiting Committee, Department of Computer Science, 4130 Upson Hall, Cornell University, Ithaca, NY 14853–7501.


Cayuga Lake Marina

USDA-ARS Computational Biologists

The US Plant, Soil, and Nutrition Laboratory, a USDA-ARS laboratory on the Cornell University campus, is seeking to fill two permanent Computational Biologist positions. One position (A) involves functional genomics of *Pseudomonas syringae*, a model system for plant pathogenesis, while the second position (B) will focus on functional genomics of crop nutritional quality and abiotic stress tolerance. Specific duties for both positions focus on sequence analysis and inference and modeling of gene regulation networks. Applications from highly motivated scientists from a wide range of relevant backgrounds are encouraged. Successful candidates will be expected to develop strong research programs utilizing both intramural and extramural funding, and form collaborations with others in the ARS lab and the broader Cornell genomics community. Candidates must have US citizenship. A PhD in an appropriate discipline is also required. The salary ranges for these positions are: $50,541 to $93,643 per annum plus benefits, depending on experience. TO APPLY: To obtain application information, visit the USDA web site at http://www.afm.ars.usda.gov/hrd/jobs/index.htm. Applicants are also encouraged to contact Drs. Dave Schneider (djs30@cornell.edu) or Jim Giovannoni (jjg33@cornell.edu) for more specific information on positions A and B, respectively. Applications in response to this ad must include the Vacancy Announcement Number ARS-X5E-0232 for position A and Vacancy Announcement Number ARS-X5E-0334 for position B. These positions will remain open until March 6, 2006.

Life Sciences / Physical Sciences Interface

Cornell has undertaken a broad-based initiative to recruit faculty and provide resources that foster multidisciplinary participation in the post-genomics era. Understanding how genes and their protein products generate the complexity and diversity that we know as life is perhaps the greatest scientific challenge of the new millennium. Developments in the physical and engineering sciences will be essential for addressing complex questions in biology and also engineering novel systems based on biological principles. At Cornell we aim to attract exceptionally talented individuals pursuing important research areas in the life sciences with quantitative, multidisciplinary approaches. Key areas of interest include:

(1) **The development and application of physical and chemical tools to study molecular events and interactions in living cells.** Examples include: the use of imaging methods (e.g., nonlinear laser-scanning microscopy) to monitor the dynamics of molecular ensembles; the application of spectroscopic and fluorescence methods to monitor protein-protein interactions; and the application of chemical synthesis to control macromolecular reactivity.

(2) **New approaches to probing molecular structure and properties.** Examples include the study and manipulation of single molecules by laser tweezers, force microscopy, or electron microscopy; and the application of protein design to understanding macromolecular interactions.

(3) **The generation of advanced materials integrating, mimicking, or expressing biological functionality.** Examples include the development, study, and/or use of new technologies in the areas of microfluidics, polymers, and biomaterials; the design of novel catalysts; and the establishment of new ways to redirect cellular activities by altering enzymatic or transport functions in organisms.

(4) **The development of new computational models and algorithms to better understand biological complexity and enhance experimental observation.** Examples include modeling of the structure and dynamics of gene networks and of signal transduction pathways, system-wide analyses of transcription and translation, and the use of computational biology to advance bioinformatics and structural biology.

Appointees will participate in the university-wide, interdisciplinary program in the life sciences (the New Life Sciences Initiative). They will be hired by and thus find their "home" in one of the following departments: Applied and Engineering Physics, Biological and Environmental Engineering, Chemical and Biomolecular Engineering, Chemistry and Chemical Biology, Computer Science, Materials Science and Engineering, Molecular Biology and Genetics, Molecular Medicine, and Physics. TO APPLY: Applicants should send, as a single PDF document, a cover letter stating the potential home department, a *curriculum vitae*, a concise statement of research and teaching interests, copies of relevant publications, and the names of at least three references to: culifesciences@cornell.edu. Review of applications will begin November 1, 2005 and continue until the positions are filled.

Molecular and Chemical Ecology

Cornell University and the Boyce Thompson Institute for Plant Research (BTI) invite applications for two faculty positions (one junior, one rank-open) in Molecular and Chemical Ecology (MaCE). We seek scientists who use molecular, chemical, genetic, genomic, biochemical, and/or proteomic approaches to study the chemical and genetic bases of interactions between animals, plants, and microbes and/or between organisms and their environment. Research areas include, but are not limited to, characterization of: molecules that mediate interactions, the receptors and pathways that transduce their signals, and behavioral, developmental, and/or metabolic responses to these molecules. Systems of interest include, but are not limited to, attractive or defensive interactions between animals (invertebrate or vertebrate), plant-microbe interactions, insect interactions with plants or microbes, and natural products chemistry. Each successful applicant will be based in the BTI or in one of the following Cornell departments: Neurobiology and Behavior, Plant Pathology, or Chemistry and Chemical Biology. MaCE faculty will join our active, interactive MaCE community, which already includes faculty in several Cornell departments and in the BTI. All MaCE faculty have access to multiple genomics and life sciences facilities on campus and are encouraged to form collaborations throughout the campus. Teaching will be appropriate to the faculty member's area of expertise and home department. TO APPLY: Application materials should be sent directly to: Dr. Maria J. Harrison, co-chair, MaCE Search Committee, Boyce Thompson Institute for Plant Research, Tower Road, Cornell University, Ithaca, NY 14853–2703. Application materials should be received by November 4, 2005. Inquiries or contacts by email should be sent to mjh78@cornell.edu.

Neuroscience

Cornell University has established a campus-wide Program in Neuroscience. Applications are invited for four junior faculty positions that use:

(1) **Cell biological approaches to study the nervous system;** individuals with this research focus will be considered as part of a broader search for an Assistant Professor of Cell Biology studying the functional organization of cells or tissues. Applicants researching focused genomic approaches to questions in cell biology are especially encouraged to apply (see details in *Science* ad of August 26 and on the first page of this ad; contact Tony Bretscher at c/o RLL2@cornell.edu for more information).

(2) **Cell biological, molecular, and/or biophysical approaches to biomedical problems in the nervous system** (contact Robert Oswald at reo1@cornell.edu for more information).

(3) **Integrative approaches to CNS function** with interests that could include, but are not limited to, the organization of sensory or motor systems; social behavior, social communication, social cognition; emotion or any other aspect of cognition such as learning and memory at the network level, spatial navigation, or decision-making. A variety of current recording or imaging techniques would be welcome (contact Barbara Finlay at blf2@cornell.edu for more information).

(4) **Developmental aspects of behavioral neuroscience,** especially social neuroscience and the analysis of genetic polymorphisms (this position is rank open; contact Richard Depue at rad5@cornell.edu for more information; for details also see the *Science* ad of August 12).

The positions are available in the departments of Molecular Biology and Genetics, Molecular Medicine, Psychology, or Human Development. Neuroscience faculty will have full access to multiple genomic and life science facilities on campus and are encouraged to form collaborations throughout the campus. TO APPLY: Applicants should send their cover letter to: Neuroscience Search, Department of Neurobiology and Behavior, Seeley G. Mudd Hall, Cornell University, Ithaca, NY 14853–2702.

East Campus Research Facility (opens 2007)

Plant Genomics

Boyce Thompson Institute for Plant Research at Cornell University

BTI, an independent, not-for-profit research organization, invites applications for tenure-track faculty positions at either the Assistant or Associate level. We are seeking candidates whose research is synergistic with that of existing faculty, but embodies new approaches or experimental areas. Examples of potentially appropriate interests are natural variation, metabolomics, proteomics, and cell biology; however, these are in no sense exclusive. BTI features state-of-the-art genomics and plant growth facilities, family-friendly policies, and a research-oriented environment. Its location on the Cornell University campus offers superb opportunities for interactions, and the development of formal links to appropriate Cornell departments is expected. TO APPLY: We particularly encourage applications from women and minorities; however, all applicants should submit a *curriculum vitae*, the names of three references and a statement of research interests (2–3 pages) to David Stern, President, Boyce Thompson Institute for Plant Research, Tower Road, Ithaca, New York 14853, 607–254–4757, or e-mail to: ds28@cornell.edu. Review of applications began August 15, and will continue until up to three positions are filled. Additional information about BTI can be obtained at http://bti.cornell.edu.

Ithaca Farmers' Market

Photographs by Cornell University Photography

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Multiple Faculty Positions in Medical Informatics and High-End Grid Computing, Bioinformatics, and Microscopic Imaging and Visualization

The Department of Biomedical Informatics (BMI) of The Ohio State University College of Medicine in The OSU Medical Center (**http://bmi.osu.edu**) seeks applications for tenure track and research track faculty at all levels in the following areas:

Medical Informatics and High End Grid Computing

BMI seeks faculty candidates with research interests in medical informatics, high-performance and grid computing systems, distributed databases, data-intensive computing, knowledge integration systems, knowledge management, and leading edge software support for translational biomedical research. The OSU Medical Center has: (1) an internationally recognized grid/data intensive biomedical computing group, (2) a comprehensive health system wide information warehouse, (3) Center for Knowledge Management and (4) informatics infrastructure that includes a deployed clinician order entry and a completely digital radiology infrastructure. The Department of Biomedical Informatics and the OSU Medical Center are committed to supporting the development of cutting-edge technologies with innovative applications in basic and translational biomedical research. Applicants should have a strong background in computer science with interest in medical applications or a clinical background in any subspecialty of medicine with substantial experience developing software to support clinical research or practice.

Bioinformatics

BMI seeks broadly trained scientists with computational research programs of biomedical relevance and collaborative potential. Programs complementing the following current research efforts in BMI and affiliated departments are of particular interest: high performance and data intensive computing, promoter and chromatin analysis, biomedical image processing and quantification, comparative genomics and phylogenetics, pharmacogenomics, cancer (including genetic and epigenetic variation), cardiovascular (including genetics and imaging), neuroscience, transplantation and critical care.

Microscopic Imaging and Visualization

BMI seeks faculty candidates with research interests in medical image analysis, computer vision, and visualization. The department is particularly interested in the areas of microscopic imaging and molecular imaging, such as light field, confocal, fluorescent, and video microscopic image analysis with biomedical applications. Applicants should have a strong background in medical imaging, microscopy, computer vision, high-dimensional data visualization, machine learning, and/or high-throughput data analysis. The Department of Biomedical Informatics has strong collaborations with researchers in the areas of radiology, pathology, cardiology, cancer, and automatic microscopic imaging. The Department is developing a framework to support computational grid-based integration and analysis of all types of studies, including Radiological and Pathological imagery. This position offers an invaluable opportunity to conduct research and education in a multidisciplinary environment.

Applications

Applicants should have a proven publication record in leading peer-reviewed journals and demonstrated potential to obtain extramural funding. Senior faculty (Associate Professor and above) should have established research programs with extramural funding. The successful applicant will have an M.D. or Ph.D. Candidates with interdisciplinary research interests are particularly encouraged to apply. Positions are open immediately, and recruitment will continue until positions are filled.

To apply, have your curriculum vitae, a brief statement of research and teaching interests, copies of 2-4 representative publications, and 3 letters of reference sent to: Biomedical Informatics at **facultypositions@lists.bmi.ohio-state.edu**. Please state whether you are applying for the Medical Informatics, Bioinformatics, or Imaging position. The preferred format for submissions is PDF, though other formats, including hard copies, will be accepted. Hard copy submissions can be sent to the following address: **Biomedical Informatics, The Ohio State University, 3168 Graves Hall, 333 W. 10th Ave., Columbus, Ohio 43210**.

The Ohio State University is an Equal Opportunity, Affirmative Action Employer.

Director of Research with Endowed Chair

The Department of Surgery at The Ohio State University Medical Center is seeking a tenured full-time faculty member at the level of Professor to direct research in the Division of Cardiothoracic Surgery. The successful candidate is an MD and/or PhD with substantial record of active extramural research funding and publications in tissue repair and remodeling. The position is supported by an endowed chair. The successful candidate will function in the rich environment of the Davis Heart and Lung Research Institute. Candidates with proven expertise in the fields of stem or progenitor cell biology, imaging or tissue engineering applied to heart failure and related problems are desirable. This position holds a co-appointment in the Biomedical Engineering program.

Applicants should send a resume and a statement of current research/funding activities to the **Chair of the Search Committee, Professor Chandan K. Sen, Vice Chairman of Research, Department of Surgery, sen-1@medctr.osu.edu. Ph: 614-247-7786, Fax 614-247-7818.**

The Ohio State University is an Equal Opportunity Affirmative Action Employer; women, minorities, and individuals with disabilities are encouraged to apply.

The Faculty of Science of the University of Fribourg/ Switzerland (Department of Medicine)

invites applications for a tenured position of

Full Professor in Biochemistry

The successful candidate will have a record of successful independent research in **Molecular Cell Biology or Biochemistry**. He/She is expected to establish an independently funded research program and to teach students of Biochemistry, Biology, and Medicine.

More information about the position, the application procedure (deadline 30.11.2005) as well as the Department, common facilities and study programs are available at www.unifr.ch/science/positions/biochemistry.php.

Kansas City University of Medicine and Biosciences invites applications for two faculty positions and an opportunity to join in an exciting institutional and regional effort to enhance life sciences research.

SENIOR FACULTY POSITION IN BIOCHEMISTRY

The Department of Biochemistry invites applications from outstanding individuals for appointment at an Associate Professor or Professor level. We seek an individual with research interests in chronic diseases of aging; applicants who can further the department's interests and activities in neurodegeneration, protein biochemistry, and biophysics are especially encouraged to apply. The successful applicant will have a Ph.D. (or equivalent doctorate), a distinguished record of scholarly publications, a track record of progressive external grant funding, be willing to mentor graduate and medical students and be able to contribute effectively to an innovative instructional curriculum. The position is available starting July, 2006. For additional information, contact Norbert Seidler, Ph.D., Professor & Chair, Department of Biochemistry, 1-800-234-4847, ext. 2207, or 816-283-2207, **nseidler@kcumb.edu**; Job #05-08.

ASSISTANT/ASSOCIATE PROFESSOR OF ANATOMY

The department of Anatomy is a clinically oriented department with an emphasis upon educational excellence. The successful candidate must have a Ph.D. in Anatomy, or related discipline, and experience teaching human gross anatomy, including full-dissection laboratory, and/or other anatomical disciplines for medical or graduate students. The candidate may elect to teach in the graduate programs in the College of Biosciences. Candidates will be expected to maintain ongoing, productive scholarly activity. Demonstrated history of extramural funding is desirable. For additional information, contact Robert E. Stephens, Ph.D., Professor & Chair, Anatomy, 1-800-234-4847, ext. 2244, or 816-283-2244, **rstephens@kcumb.edu**; Job #05-40.

FOR BOTH POSITIONS

KCUMB, an expanding institution with an emerging emphasis on research and health maintenance, recently completed a 46,000/sq.-ft.-building for bioscience research. We are Missouri's largest medical school and strive to hire outstanding faculty & staff to provide an exemplary education for approx. 1,000 graduate and osteopathic medical students. Excellent pay is complemented with an exceptional benefits package. We are located in the historic Northeast part of Kansas City, MO, near downtown and collaborating institutions.

To apply, send a letter of interest w/job#, curriculum vitae, statement of research, teaching goals and philosophies, and contact information for 3 references to: Susan M. Schmidt, Asst. Director of Employment Services, 1750 Independence Ave., Kansas City, MO 64106-1453, 1-800-234-4847, ext. 2229 or 816-283-2229; or e-mail **employment@kcumb.edu** (Word or PDF format only please), or fax 816-283-2285. Pre-employment drug screen and background check required. Must be a citizen, permanent resident, or otherwise permanently authorized to work in the USA. EOE. **www.kcumb.edu.** KCUMB is a key stakeholder and an integral part of the Kansas City Area Life Sciences Institute. **www.kclifesciences.org**

KANSAS CITY UNIVERSITY OF MEDICINE & BIOSCIENCES

ScienceCareers.org

CARDIOVASCULAR BIOLOGY PROGRAM HEAD

■ The Oklahoma Medical Research Foundation seeks a new Head for one of its most successful research programs. OMRF is an independent, non-profit research institute located adjacent to the University of Oklahoma Health Sciences Center campus in Oklahoma City and a thriving research park is nearby. It has a proud 59 year history and is recruiting in several areas to continue its record of success. OMRF scientists work in an extremely supportive and affordable community.

■ The nine investigators in this group include one who is an HHMI Investigator and Member of the National Academy of Sciences. They populate the Editorial Boards of such journals as The Journal of Biological Chemistry, The Journal of Clinical Investigation, and Blood. In addition, they are members of scientific professional and honor societies such as the American Society of Clinical Investigation. The Cardiovascular Biology program currently attracts nearly $7M in extramural research funding/year out of approximately $35M for OMRF as a whole. Many patents and successful drugs have been developed by this team and further details of their current work can be found at: http://www.omrf.org/OMRF/Research/15/Welcome.asp

■ OMRF enjoys the finest in laboratories, equipment and core facilities, including microarrays, signal transduction, biological imaging, DNA sequencing, gene targeting, and cell sorting, as well as a new state-of-the-art small animal vivarium and MRI facility. Additional information about these resources, can be found at: http://www.omrf.org/OMRF/Core/Welcome.asp

■ The successful candidate may work in one of several areas relating to cardiovascular biology, such as genetics, vascular biology, inflammation, development, sepsis, regenerative medicine and stem cell biology. These are just examples, and the search committee is principally interested in leadership potential. Scientific excellence and a record of distinguished productivity will of course be important.

■ Confidential inquiries and resumes may be directed to: Dr. Paul W. Kincade, Chair of the search committee, OMRF, 825 N.E. 13th Street, Oklahoma City, OK 73104 or care of: wassons@omrf.ouhsc.edu

FOR MORE INFORMATION, VISIT www.OMRF.org

OMRF
Oklahoma Medical Research Foundation
825 NE 13th Street Oklahoma City, OK 73104-5046 • www. OMRF.org

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NANYANG TECHNOLOGICAL UNIVERSITY

School of Physical & Mathematical Sciences

Faculty Appointments

The Nanyang Technological University's School of Physical and Mathematical Sciences invites applications for full-time tenure-track faculty positions at all ranks, with preferred areas in its three Divisions as follows:

Division of Chemistry & Biological Chemistry

- Synthesis Methodology & Catalysis
- Physical/Theoretical/Computational Chemistry
- Medicinal/Green Chemistry
- Analytical Chemistry
- Bioorganic/Bioinorganic/Biophysical Chemistry

Division of Mathematical Sciences

- Statistics & Probability
- Computational Mathematics & Applications
- Discrete Mathematics & Applications
- Pure Mathematics
- Operations Research
- Interdisciplinary Science with significant mathematical content

Division of Physics & Applied Physics

- Biophysics and Bio-medical Physics
- Laser Physics, Photonics and Atom Optics
- Condensed Matter and Soft-condensed Matter Physics
- Nanoscience, Surface Science and Low Dimensional Systems
- Quantum Computing and Quantum Information Technology
- Semiconductor Physics, Spintronics, Organic Electronics

As NTU is a Doctoral/Research University, applicants should have a PhD and preferably post-doctoral experience in the discipline from a major research university. Successful applicants are expected to teach graduate and undergraduate courses, undertake curriculum development, supervise doctoral students, develop outstanding research programs that generate external funding, and perform essential administrative work. Applicants should send (by e-mail or post) an application letter, a CV, a research plan, and names and addresses of three referees to:

School of Physical & Mathematical Sciences
NANYANG TECHNOLOGICAL UNIVERSITY
1 Nanyang Walk, Blk 5, Level 3, Singapore 637616
Tel : (65) 6790 3712 Fax : (65) 6316 6984
Email: claire@ntu.edu.sg

Note: Only shortlisted candidates will be notified.

GKSS FORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Grundlagen für morgen

Unternehmen Großforschung

The GKSS Research Centre is located in Geesthacht near Hamburg with a further centre in Teltow near Berlin, and is a member of the Helmholtz Association of German Research Centres. With its approximately 700 employees it undertakes, in collaboration with universities and industry, research and development in the areas of materials research, coastal research, regenerative medicine, and structure research with neutrons and synchrotron radiation.

GKSS operates the Geesthacht Neutron Facility GeNF using the reliable medium flux neutron source FRG-1 (http://genf.gkss.de) and is currently creating a centre for materials research based on the complementary use of synchrotron and neutron radiation. Important topics of our applied research are, among others, the investigation of lightweight structural materials by diffraction (strains, textures) and tomography as well as metallic and polymer nanostructures by small angle scattering and reflectometry. In the framework of a strategic collaboration with the HGF institution DESY (Hamburg) we are currently in the commissioning phase of a synchrotron beamline for high energies at the storage ring DORIS at DESY. In addition we operate a growing outstation at the new neutron source FRM II in Munich currently focussing on neutron reflectometry and texture analysis and in future also on strain analysis and small angle scattering. In this framework we have three openings:

As a next step of our engagement at DESY we will construct a further high energy materials science beamline at the new dedicated 3rd generation synchrotron light source PETRA III. For this new high energy materials science beamline at DESY we are looking for a

Scientist - Code-No. W 8

who should have experience in the planning, construction and operation of 3rd generation synchrotron beamlines. One of your major tasks will be the development and implementation of experimental techniques for materials characterisations with high spatial and time resolution both for diffraction and imaging methods. This involves in particular the development of microfocussing optics for high energy synchrotron radiation. You will have a leading role at this beamline and will be responsible for its smooth operation. After commissioning an important part of your mission is to assist beamline users and to efficiently carry out orders from industry. In addition we expect your active involvement in the materials science research program of GKSS.

In addition we are looking for a

Scientist (Postdoc) - Code-No. W 9

(initial three-year contract) in the field of residual stress analysis with diffraction methods. You will be responsible for one of our neutron diffractometers for residual stress analysis. In this position you will take care of external users of our facility at Geesthacht as well as deal with scheduled orders from industry. Opportunities for gaining additional qualifications by cooperation with internal partners, especially in the field of joining techniques, are available. Current topics in this field are friction stir welding as well as laser beam welding for aircraft construction. In addition, you will also deal with fundamental problems of diffraction-based stress analysis. Ideally, you already have a working knowledge in the mechanics of materials and experience with diffraction methods for residual stress analysis.

Furthermore, we are looking for a

Scientist (Postdoc) - Code-No. W 10

(initial three-year contract) in the field of nanomagnetism who should have experience with polarised neutron reflectometry and diffuse scattering which are used for the study of vertically and laterally structured magnetic and non-magnetic nanostructures. You will be responsible for one of our neutron reflectometers in Geesthacht with the mission to take care of external users. In addition you will be integrated into exciting research efforts in the fast moving field of nanomagnetism in cooperation with external partners.

A fast familiarization with new topics is a personal challenge for all of you. Use of complex experiments and control software is no challenge for you. Your English communication skills are good; German language skills are an asset. You have adopted a purposeful and result-oriented way of working and are able to realize this in a team. You are flexible and communicative in your approach with collaborators and you give priority to the success of a project and your team. You are used to publishing the results of your work and presenting them at international conferences.

A Ph. D. or equivalent in a field relevant to one of the research areas listed above (e.g. physics, materials science, crystallography, chemistry …) is mandatory. We offer an appropriate salary, related to BAT as well as the usual public sector social benefits.
In order to increase the number of female employees we ask interested and qualified women to apply for the job. Handicapped persons with equal qualifications will be preferred.

For inquiries please contact Prof. Andreas Schreyer (andreas.schreyer@gkss.de).

Please send your application including CV and references within 14 days from the date of publication to the email address given above or to:

GKSS-FORSCHUNGSZENTRUM GEESTHACHT GMBH • PERSONALABTEILUNG • MAX-PLANCK-STR. 1 • 21502 GEESTHACHT

ScienceCareers.org

ASSISTANT-ASSOCIATE-FULL PROFESSOR STRUCTURAL BIOLOGY – CANCER DRUG DISCOVERY

The College of Medicine and the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida are seeking candidates for Assistant, Associate, or Full Professor level individuals to participate in the Department of Interdisciplinary Oncology and the Drug Discovery Program. This tenure track faculty position will be at a rank that is commensurate with the qualifications of the successful candidate.

Applicants must have a demonstrated track record in research areas related to structural biology with emphasis on X-ray crystallography and the elucidation of structure-function relationships. Areas of research focus could include protein structure-function relationships, protein/drug interactions and protein/protein interactions. Experience in the areas of growth factor signal transduction, proteins involved in oncogenesis or tumor suppression, and cell cycle regulation preferred. Applicants should have a strong desire to interact with scientists engaged in drug discovery and design, including synthetic organic chemists and computational chemists.

Prerequisites for the rank of Assistant Professor include a Ph.D. degree and at least two years of post-doctoral experience or equivalent. Individuals at the rank of Associate Professor must possess a demonstrated potential for extramural funding. The academic rank of Associate Professor normally requires a minimum of five years of continuing and productive service as an Assistant Professor in a university setting or equivalent. Individuals applying for the Full Professor position must have a proven track record of independent research, leadership and training as evidenced by publications and extramural funding. The academic rank of Professor normally requires a minimum of five years of continuing and productive service as an Associate Professor in a university setting or equivalent.

The Moffitt Cancer Center and Research Institute, a National Cancer Institute-designated comprehensive cancer center, and USF offer an outstanding salary, benefits and relocation package. Academic rank and salary will be commensurate with experience and qualifications. This tenure track position will be assigned to the Department of Interdisciplinary Oncology within the College of Medicine.

Please reference position no. DIO0520. Applicants should submit a letter of intent and curriculum vitae to Dr Saïd Sebti, c/o Dr. Wayne C. Guida, Chair, Structural Biology Search Committee, Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, SRB-3 DRDIS, 12902 Magnolia Drive, Tampa, FL 33612-9497; guidawc@moffitt.usf.edu. The position is open until filled. Application review begins October 1, 2005.

H. LEE MOFFITT Cancer Center & Research Institute

The End Of Cancer Begins Here.

A National Cancer Institute Comprehensive Cancer Center
At the University of South Florida

USF University of South Florida
College of Medicine

The University of South Florida is an EO/AA/EA institution. For disability accommodations, contact Kathy Jordan (813-632-1451) a minimum of five working days in advance. According to Florida law, search records, including applications and search committee meetings, are open to the public.

www.moffitt.usf.edu

Department of Physiology
Tenure Track Faculty Positions

The Department of Physiology at The University of Texas Health Science Center at San Antonio (UTHSCSA), under new leadership, will be undergoing a major expansion over the next several years. This round, we seek to fill two tenure track faculty positions to begin by August 2006. The intention is to hire Assistant Professors, but exceptional candidates at more senior levels will be considered. At present, Physiology has clusters of research strength in neuroscience, cardiovascular function, ion channel biophysics, and the molecular biology of aging. Although candidates that can extend or bridge these areas are encouraged to apply, we are most interested in talented investigators using cutting edge techniques and/or model systems to elucidate fundamental physiological mechanisms at the molecular, cellular, or integrative levels. Candidates will be expected to contribute to the teaching mission that includes training medical, dental, and graduate students.

UTHSCSA is a Tier I Research Institution and the Department of Physiology is currently ranked 17th out of 98 in NIH funding. Plans and resources are in place to continue to grow the university as a whole and the Department of Physiology in particular. Competitive start-up packages and ample resources will be offered to those selected to be part of this exciting endeavor. UTHSCSA is located in the Northwest region of San Antonio and is a gateway to the picturesque Texas Hill Country. San Antonio is a vibrant, dynamic, multicultural city with much to offer including an attractive cost-of-living.

Candidates should submit a Curriculum Vitae and research accomplishments/goals (not to exceed two pages) as a single PDF to:

David S. Weiss, Ph.D., Professor and Chair
Department of Physiology
E-Mail: PhysioSearch@uthscsa.edu
Website: http://physiology.uthscsa.edu

Also, arrange for three letters of recommendation to be forwarded to the above e-mail address. Candidates that wish to be considered for this position should ensure that their applications are complete by **November 28, 2005**.

All faculty appointments are designated as security sensitive positions. The University of Texas Health Science Center at San Antonio is an Equal Employment Opportunity/Affirmative Action Employer.

The Lerner Research Institute of the Cleveland Clinic Announces the Formation of a New Department of Stem Cell Biology and Regenerative Medicine

We are seeking an established or "emerging leader" stem cell scientist/mammalian developmental biologist to direct our newly created Department. This Department will grow to 10 to 12 faculty and occupy ~25,000 sq. ft. in a new wing of the Lerner Research Institute. The Department will augment strengths in the areas of hematopoietic, cardiovascular, neuroscience and connective tissue stem cell research. The ideal applicant for this position will have a productive research program in fundamental or translational aspects of stem cell and developmental biology and a vision for creating a unique, world-class department. This Department is part of the state-funded Cleveland Center for Stem Cell and Regenerative Medicine involving the Cleveland Clinic, Case Western Reserve University, University Hospitals of Cleveland and several corporate partners. The Chair will be provided with a highly competitive, institutionally supported salary, generous start-up funds, and recruitment packages for new faculty.

The Lerner Research Institute with over 120 principal investigators and an annual budget of over $105 million ($73M from NIH) has a commitment to excellence in basic and translational biomedical research.

A letter of interest and curriculum vitae should be e-mailed or sent to:

Paul E. DiCorleto, Ph.D.
Cleveland Clinic Lerner Research Institute, NB21
9500 Euclid Avenue
Cleveland, Ohio 44195

E-mail: dicorlp@ccf.org
http://www.lerner.ccf.org

THE CLEVELAND CLINIC

U.S. Department of Health and Human Services
Food and Drug Administration

CAREER OPPORTUNITIES

Be a part of discovery! Help shape the future of Medicine! Make a difference for the American public!
Take the next step in your career! The opportunity is NOW!!

The Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs is recruiting **PHYSICIANS, SCIENTISTS,** and **CONSUMER SAFETY OFFICERS** to serve in the dynamic, highly challenging and innovative atmosphere of drug development and research. The Office of New Drugs public health mission is to protect and enhance the health of the public through the review and evaluation of scientific data submitted by pharmaceutical manufactures in support of New Drug and Investigational New Drug applications (NDA/IND), and render an approval or disapproval for human use.

GENERAL INFORMATION: The following positions may be filled as civil service or U.S. Commissioned Corps which requires U.S. citizenship. Permanent U.S. residents may apply for Staff Fellowship appointments in physician and scientist positions. Graduates of foreign colleges/universities must provide proof of U.S. education equivalency certification. Employment opportunities offer competitive salaries and excellent benefits.

PHYSICIANS (Various medical specialties): Evaluate data involving the animal testing and human clinical trials of new drugs to determine their safety and effectiveness. Basic Requirements: Degree: Doctor of Medicine or Doctor of Osteopathy from a school in the United States or Canada approved by a recognized accrediting body in the year of the applicant's graduation. [A Doctor of Medicine or equivalent degree from a foreign medical school that provided education and medical knowledge substantially equivalent to accredited schools in the United States may be demonstrated by permanent certification by the Educational Commission for Foreign Medical Graduates (ECFMG) (or a fifth pathway certificate for Americans who completed premedical education in the United States and graduate education in a foreign country).] Civil Service Salary GS-14, $88,893-114,882, plus an additional Physicians Comparability Allowance may also be paid.

SCIENTISTS: Scientists evaluate portions of INDs/NDAs that pertain to their particular discipline. They determine the scientific validity of manufactures' tests, and evaluate drug safety and efficacy claims. Civil Service Salary, GS-12, $62,886-81,747/ GS-13, $74,782-97,213. An advanced degree in a relevant biological science, such as a Ph.D. or D.V.M, is highly desirable.

- **Pharmacologists:** Basic Requirements: A degree with a major in an appropriate biological, medical, veterinary, or physical science, or in pharmacy that included at least 30 semester hours in chemistry and physiology and 12 semester hours in pharmacology.
- **Toxicologists:** Basic Requirements: Degree: toxicology; or an appropriate discipline of the biological, medical, or veterinary sciences that included at least 30 semester hours in chemistry, biochemistry, or physiology, and 12 semester hours in toxicology.
- **Biologists:** Basic Requirements: Degree: biological sciences, agriculture, natural resource management, chemistry, or related disciplines appropriate to the position.
- **Microbiologists:** Basic Requirements: Degree: microbiology; or biology, chemistry, or basic medical science that included at least 20 semester hours in microbiology and other subjects related to the study of microorganisms, and 20 semester hours in the physical and mathematical sciences combining course work in organic chemistry or biochemistry, physics, and college algebra, or their equivalent.

CONSUMER SAFETY OFFICERS: Perform management and liaison responsibilities in conducting records maintenance, monitoring the work effort and advising review team members on regulatory requirements, and coordinating information with pharmaceutical industry officials. *Basic Requirements:* a degree or combination of education and experience which includes at least 30 semester hours in one or a combination of courses in the fields of biological science, chemistry, pharmacy, physical science, food technology, nutrition, medical science, epidemiology, engineering, veterinary medical science, or related scientific fields. Project management experience in the healthcare/pharmaceutical industries is highly desired for these positions. Civil Service Salary, GS-9, $43,365-$56,371/GS-11, $62,886-81,747 /GS-12, $62,886-81,747

HOW TO APPLY: Submit curriculum vitae with cover letter via e-mail by **October 31, 2005** to: **Employment@cder.fda.gov** indicating you are applying to **source code # 05-001-6** or send hard copies to:

U.S.FDA
Center for Drug Evaluation and Research
Office of New Drugs/
Program Management Team
Attn: Dwayne Keels
10903 New Hampshire Ave, Bldg#22, Rm 6445
Silver Spring, MD 20993

For more information, contact the Office of New Drugs/Program Management Team at 301-796-0800.

THE FDA IS AN EQUAL OPPORTUNITY EMPLOYER WITH A SMOKE FREE ENVIRONMENT

ScienceCareers.org

www.gojobs.gov.on.ca

MEDICAL MICROBIOLOGISTS

Join a team of professionals making significant organizational changes leading to a revitalized public health laboratory system for Ontario. The **Ministry of Health and Long-Term Care** seeks five individuals to provide medical leadership, oversee diagnostic services (e.g., virology, molecular diagnostics) and lead relevant research. Reporting to the medical director, you will: provide medical advice with respect to disease outbreaks/public health emergencies; contribute to policy development/strategic plans in support of Ontario's public health laboratory system; participate in investigative studies/projects, with links to the academic health sciences centres/universities. Salary is negotiable. **Location: 81 Resources Rd., Toronto, Ontario, Canada.**

Qualifications: medical degree; Ontario medical licence or equivalent; specialization in medical microbiology from the Royal College of Physicians/Surgeons of Canada (or equivalent); demonstrated expert knowledge in medical microbiology; leadership skills; demonstrated planning/organization skills to support the public health laboratories system.

Resume and covering letter must be received by Oct. 24, 2005. Quoting file HLC1180-05, send to: Ministry of Health and Long-Term Care, Human Resources Branch, Client Services, 5700 Yonge St., 2nd Fl., Toronto, Ontario, Canada, M2M 4K5. Fax: 416-326-4107. E-mail (MS Word format, only; quote file number in the subject line): hropenresumes@moh.gov.on.ca. *Application must be received by the closing date. Only those applicants selected for an interview will be contacted.*

Ontario

An equal opportunity employer

RESEARCH ASSOCIATE/ASSISTANT PROFESSOR

The University of Chicago, Department of Pathology, is seeking a full-time Research Associate (Assistant Professor) to study the cellular immunology and the biochemistry of lipid antigen presentation by CD1 molecules in the context of infectious diseases. Applicants should have a strong background in biochemistry and glycobiology and should be able to design and conduct experiments independently. Candidates must have the ability to prepare and present their work at international meetings, to write scientific manuscripts and grant applications. A Ph.D. in Medicine with training in microbiology and infectious diseases is preferred, with at least 5 years research experience in the field. Publication record must include several first-author papers in top scientific journals.

Qualified applicants must provide current CV and bibliography, statement of research interest and goals, full names, addresses, telephone/fax numbers, and e-mail addresses of at least three scholars who can provide academic references to M. Blunt, University of Chicago, 5841 S. Maryland, MC 3083, Chicago, IL 60637. The University of Chicago is an EOE M/F/D/V

UCSD

ASSISTANT PROFESSOR
Pharmacology/Biochemistry

The University of California, San Diego invites applications for a tenure-track position at the Assistant Professor level in the Departments of Pharmacology and Chemistry/Biochemistry. Applicants must hold a Ph.D. and/or M.D. degree. Candidates whose fields of interest include mechanisms of cell signaling, membrane biophysics or biochemistry, or molecular specificity of therapeutic agents will be given the strongest consideration. Incoming faculty must be willing to teach biochemistry or related areas to graduate and professional students (M.D., Pharm. D., Ph.D.), mentor thesis studies of Ph.D. students and carry out a scholarly and contemporary research program. Incumbent will be expected to conduct an extramurally funded research program involving graduate students and postdoctoral fellows, and participate in administrative functions of the departments and the University. Candidates will be expected to show evidence of their potential through letters of recommendation and a publication record appropriate for their experience. Salary will be commensurate with qualifications and experience in accordance with UCSD policy.

Applications accepted until **November 30, 2005**. To apply, send curriculum vitae, summary of current and future research plans, reprints of significant publications, and names of at least three individuals who will write recommendation letters. Please ask that they be sent immediately and direct all materials to:

Chair, Search Committee (SC2005)
Department of Pharmacology
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093-0636

UCSD is an Affirmative Action/Equal Opportunity Employer committed to excellence through diversity.

University of Central Florida
Faculty Position in X-ray Crystallography

The University of Central Florida (UCF) invites applications for a tenure track-faculty position at any rank for a joint appointment between the Department of Chemistry (**http://www.cas.ucf.edu/chemistry**/) and the Biomolecular Science Center (**http://www.bmsc.ucf.edu**/). Candidates should have expertise and interest in working on proteins of biomedical importance with chemists and molecular/cell biologists in a collaborative environment. A Ph.D. and 2-3 years of post-doctoral experience in the determination of protein structures is required. Candidates at the higher ranks must have a demonstrated record of accomplishments in extramural funding, publication, and teaching. Exceptionally outstanding candidates may be considered for a Provost's Research Excellence Professorship. In addition to contributing to teaching at both the graduate and undergraduate levels, applicants are expected to establish a nationally recognized research program, and participate in the Ph.D. programs in Chemistry and Biomolecular Science. The successful candidate will have the opportunity to develop interactions with UCF's research centers, including CREOL (**http://www.creol.ucf.edu**/), Biomolecular Science, Nanoscience (**http://www.nanoscience.ucf.edu**/), and other departments within the university.

The University of Central Florida is located in Orlando, Florida and has become one of the nation's largest universities with 45,000 students and is continuing to build nationally recognized research programs. Applicants should submit a curriculum vitae, description of their research plans, graduate/undergraduate course teaching interests, teaching philosophy, and have three letters of recommendation sent on their behalf to: **Biochemistry Search Committee, c/o Dr. Thomas Selby, Department of Chemistry, University of Central Florida, Orlando, FL 32816-2366** or send via email to: **tselby@mail.ucf.edu**. Review of applications will begin **November 15, 2005** and continue until the position is filled.

The University of Central Florida is an Equal Opportunity Employer and welcomes nominations and applications from women and minority group candidates. UCF makes all application materials (including transcripts) available for public review upon request.

Friedrich Miescher Institute

FMI

Group Leader Position – Growth Control

The Friedrich Miescher Institute invites applications for a tenure track group leader position in the Growth Control Programme. We are seeking an outstanding individual who will establish a vigorous and ambitious research programme aimed at fundamental questions in Cancer Biology. We are particularly interested in individuals who focus on signalling pathways and metastasis.

The Institute provides excellent core facilities for genomics, protein chemistry and proteomics, monoclonal antibody production, fluorescence-activated cell sorting, fluorescence imaging, histology and mouse genetics. A highly competitive start-up package will be provided. The Friedrich Miescher Institute, part of the Novartis Research Foundation, is an international biomedical research centre with 280 members, including 180 post-doctoral fellows and graduate students (for further information see www.fmi.ch).

The Friedrich Miescher Institute is situated in Basel, Switzerland, a city offering an outstanding scientific and cultural environment in the centre of Europe.

Formal applications, including a CV, names and contact details of three referees and a concise description of research interests and future plans should be addressed to:

Professor Susan Gasser, Director
Friedrich Miescher Institute
Maulbeerstrasse 66
4058 Basel, Switzerland

The closing date for applications is:
December 1st, 2005

EPFL
ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Dean of Engineering

at Ecole Polytechnique Fédérale de Lausanne (EPFL)

EPFL is conducting an international search for the Dean of the School of Engineering to take office by the fall of 2006. EPFL is a leading European University and a growing, dynamic, well-funded institution with a focus on engineering, computer & communication, basic and life sciences. The School of Engineering, with 43 faculty members, has a tradition of excellence in the fields it encompasses: electrical, mechanical, and micro-engineering. It interacts closely with the other schools at EPFL to foster education, at the bachelor, master and doctoral levels, and transdisciplinary research.

The Dean reports to the President of EPFL. The ideal candidate has an outstanding academic record, proven leadership and management ability, and a strong vision for research, teaching, and industrial developments.

The School of Engineering Dean Search Committee invites letters of nomination, applications (vision statement, complete CV, and the name of at least 5 professional references), or expressions of interest to be submitted by **October 28th, 2005**. Materials and inquiries should be addressed, preferably electronically (PDF format) to:

Prof. Giovanni De Micheli
Chairman of the Search Committee
EPFL - INF 341 – Station 14
CH-1015 Lausanne, Switzerland
Phone +41.21.693.0911
e-mail: giovanni.demicheli@epfl.ch

More information on EPFL and the school of engineering can be found at http://www.epfl.ch and http://sti.epfl.ch respectively.

EPFL is an equal opportunity employer.

Metabolic Biology

The newly formed Center for Metabolic Biology, a multidisciplinary group of basic scientists, and the School of Life Sciences at Arizona State University invite applications for a tenure-track position (with appointment at the Assistant or Associate Professor level) from individuals who will join in the Center's mission to unravel the mechanisms underlying insulin resistance, obesity, vascular disease, and type 2 diabetes mellitus. This position is part of a major expansion in the life sciences at Arizona State University, the ongoing development of the Biodesign Institute at Arizona State University (**http://www.azbio.org/**) and the partnering of ASU with the Translational Genomics Research Institute (TGEN), the Carl Hayden VA Medical Center, and the Mayo Clinic Scottsdale.

Candidates must have a doctoral degree in a related discipline at the time of appointment, experience in teaching and research appropriate to rank, and at least two years of postdoctoral research experience in a relevant discipline. Preferred areas of expertise are functional genomics or proteomics, phenotyping and characterizing mouse models, and generation and use of such models to address questions of altered gene expression or insulin signaling in insulin resistance. Research areas could include the role of inflammatory response, lipids, or mitochondrial dysfunction in insulin resistance. The successful candidate is expected to develop an innovative, extramurally funded and independent research program, participate in undergraduate and graduate education in the School of Life Sciences, mentor undergraduates and postdoctoral fellows, as well as interact in the multidisciplinary Center for Metabolic Biology. The successful candidate will receive a competitive start-up package and teaching load compatible with research productivity.

To apply, send a cover letter, a curriculum vitae, statements of future research plans and teaching philosophy and interests. Additionally, for an associate professor level position, include the name, phone number and email address for 3 references; for the assistant professor level, request 3 letters of recommendation to be sent. Letters of reference, but not application materials, may be sent by email. The closing date for receipt of applications is **October 31, 2005**; if not filled, applications will be evaluated weekly thereafter until the search is closed. Anticipated start date is August 16, 2006. Send applications and email inquiries to: **Chair, Metabolic Biology Search Committee, School of Life Sciences, PO Box 874501, Arizona State University, Tempe, AZ 85287-4501; email: sols@asu.edu**. A background check is required for employment.

ASU is an Affirmative Action/Equal Opportunity Employer.

Tenure Track Faculty Positions in Human Genetics

The Department of Human Genetics of the Mount Sinai School of Medicine of New York University invites applications for tenure-track faculty. We seek PhD, MD, and/or MD/PhD faculty with an interest in joining a large and active basic, and clinical research program in genetics. Individuals with strong research programs and a track record of funded research and publications in the following areas are encouraged to apply: genomics and gene discovery, statistical genetics/genetic epidemiology, genetics of aging, epigenetics, chromosome structure/function, cancer genetics, biochemical or molecular mechanisms of disease, treatment of genetic disease, and stem cell biology. Positions are available at all ranks, commensurate with experience. Generous start-up packages and space are available. Applicants should forward their curriculum vitae, a statement of research plans, current grant support, and two or three references to: **Robert J. Desnick, PhD/MD, Professor and Chairman, The Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1498, New York, NY 10029, email: Robert.Desnick@mssm.edu.** Mount Sinai is an equal opportunity employer.

Laboratory for Drug Discovery in Neurodegeneration Harvard Center for Neurodegeneration & Repair

Research Fellowships in Drug Discovery

Request for Applications

The Laboratory for Drug Discovery in Neurodegeneration (LDDN) is a core program of the Harvard Center for Neurodegeneration & Repair and has a mission to identify chemical agents that can be used as lead structures for the development of therapeutics. To discover these compounds, LDDN screens their large collection of drug-like molecules for the ability of these compounds to modulate the biological activity of molecular and cellular processes that are thought to play causative roles in neurodegenerative diseases. Optimization of these compounds is achieved by focused programs of medicinal chemistry. To facilitate these activities, the LDDN has a permanent staff of a dozen scientists with industrial experience in assay design, high-throughput screening, informatics, and medicinal chemistry.

The LDDN was recently awarded a grant from the NINDS Cooperative Program in Translational Research that allows us to establish a Fellowship Program in Drug Discovery Research. The goal of this program is to provide postdoctoral fellows, and in some cases graduate students, the unique opportunity to work in a biotech-like atmosphere and transform their basic neurobiological findings into drug discovery programs.

Funding is available for five fellowships and will cover salary, supplies and a housing allowance for the fellows to reside in Boston area for a period of one year. The proposed drug discovery project should be based on on-going studies of the applicant and mentor, and have clear relevance for neurodegenerative disease. If you are interested, please visit our website (**http://www.hcnr.med.harvard.edu/**) where you will find further details about the program and detailed instructions on how to apply. Applications are due **January 15, 2006**. Decisions will be announced March 2006, for a start date of September 1, 2006. General enquiries can be sent to Eiblis Goldings, Administrative Assistant, LDDN at **egoldings@rics.bwh.harvard.edu**.

ASSISTANT PROFESSOR

Arizona State University
School of Life Sciences
Center for Biology and Society

Philosophy of Biology/Epistemology

The School of Life Sciences invites applications for a tenure-track Assistant Professor. The successful candidate will participate in teaching and research in interdisciplinary programs in History and Philosophy of Science and related areas. Candidates must (1) exhibit potential for a distinguished record of scholarship, through publications and professional presentations; (2) demonstrate teaching experience and promise for excellence in teaching; (3) show potential for participating in funded research; and (4) show potential for collaborations with individuals doing research in the life sciences; and (5) applicants must hold a doctorate with specialization in philosophy of science or history and philosophy of science, especially the life sciences.

A successful candidate will be a broadly trained philosopher of science with special expertise in epistemology, philosophy of evolutionary biology and/or complex systems, history of science and substantive grounding in the life sciences. Salary and start up support are competitive, commensurate with experience, and appropriate to research area.

To apply, submit a cover letter outlining career goals, your curriculum vitae, a statement of current research experience and future interests, and a statement detailing teaching philosophy, interests and experience, and request 3 letters of recommendation to be sent. *Letters of reference, but not application materials, may be sent by email*. Send material to: **Chair, Philosophy of Biology/Epistemology Search Committee, School of Life Sciences, PO Box 874501, Arizona State University, Tempe, AZ 85287-4501. Email sols@asu.edu**. Initial closing date for applications, including letters, is **November 10, 2005**; if not filled, weekly thereafter until search closed. Anticipated start date is August 16, 2006. A background check is required for employment.

Arizona State University is an Equal Opportunity/ Affirmative Action Employer.

THE UNIVERSITY of LIVERPOOL

Department of Chemistry

The Liverpool Materials Chemistry Group has recently been awarded Portfolio Partnership support by the EPSRC for Complex Materials Discovery. This is a multidisciplinary research programme which offers a broad range of opportunities in materials synthesis and characterisation.

6 Postdoctoral Positions in Materials Chemistry

£25,633 - £29,715 pa (under review)

Positions are available in inorganic, organic and hybrid materials synthesis and characterisation. Specific areas of interest are: physics of new electronic and magnetic materials; oxide film growth by pulsed laser deposition; ionic (oxide and proton) and mixed conducting materials; synthesis of new fulleride materials; synthetic oxide chemistry; high pressure synthesis; polymer synthesis; surfactants; chemometrics; organic synthesis; supercritical fluids; nanoparticles and colloids as "building blocks" for higher-order structures; metal-organic and inorganic nanoporous materials. It should be noted that applications from well-qualified candidates with interests in other areas are also encouraged. A PhD in chemistry, materials science or physics and an excellent publication record are essential, with skills in the specific areas identified above desirable. The appointments will be for one year in the first instance with possible extension of up to two years.

Quote Ref: B/582/S **Closing Date: 21 October 2005**

Further particulars and details of the application procedure should be requested from the Director of Personnel, The University of Liverpool, Liverpool L69 3BX on 0151 794 2210 (24 hr answerphone), via email: jobs@liv.ac.uk or are available online at http://www.liv.ac.uk/university/jobs.html

COMMITTED TO EQUAL OPPORTUNITIES

Massachusetts Institute of Technology

The Biology Department of the Massachusetts Institute of Technology is conducting searches for multiple tenure-track faculty positions at the Assistant Professor level, which will be located in the Koch Biology Building, the Broad Institute, the Center for Cancer Research, and the Whitehead Institute. We encourage women and minority scientists to apply for these positions. Applicants should have the ability to develop a world-class research program in modern biology or biomedical research and should be committed to undergraduate and graduate education.

Each applicant should submit a *curriculum vitae*, a summary of current and proposed research, and arrange for three letters of recommendation to be sent to one of the search committees listed below. Interested candidates may apply to multiple searches. Consideration of completed applications will begin on **October 15, 2005**.

Biological Mechanisms: Areas of interest include the mechanisms of fundamental biological processes studied using the tools of biochemistry, molecular biophysics, chemical biology, or structural biology. **Biological Mechanism Search Committee; attn: R.T. Sauer, MIT 68-571, 77 Massachusetts Avenue, Cambridge, MA 02139.**

Biological Interactions and Pathways: Areas of interest include cell biology, developmental biology, neurobiology and evolutionary biology. Proposed research programs should involve physiologic, genomic or other systems approaches to the study of cells or organisms or the interactions between cells or between organisms. **Biology Search Committee; attn: H.R. Horvitz, MIT 68-132, 77 Massachusetts Avenue, Cambridge, MA 02139.**

Cancer Biology: Areas of interest in the general area of experimental cancer biology include signal transduction, mechanisms of oncogene and tumor suppressor action, proteomics, chemical biology, systems biology, cellular communication, migration and metastasis, angiogenesis, and stem cell biology. **CCR Search Committee; attn: M.B. Yaffe, MIT E17-110, Center for Cancer Research, 77 Massachusetts Avenue, Cambridge, MA 02139.**

Biological Paradigms: Candidates should be pursuing fundamental problems in molecular, cellular, or organismal biology involving vertebrate or invertebrate systems. Areas of interest include but are not limited to development, genetics, and disease models. **Whitehead Search Committee; attn: D.C. Page, Whitehead Institute for Biomedical Research, Nine Cambridge Center, Cambridge, MA 02142-1479.**

Genomic Medicine: Applicants should have wide-ranging interests in comprehensive approaches to biological systems and disease biology, studied in humans or model organisms using the tools of molecular biology, genomics, medical genetics, chemistry, computational science, and/or engineering. **Broad Search Committee; attn: E.S. Lander, MIT 68-132, 77 Massachusetts Avenue, Cambridge, MA 02139.**

MIT offers a comprehensive benefit package that includes: housing assistance, medical, dental, disability and life insurance, 401(k) and pension plan. Web page: **http//web.mit.edu/biology**.

MIT is an Equal Opportunity Affirmative Action Employer.

ScienceCareers.org

FELLOWSHIPS

LAWRENCE POSTDOCTORAL FELLOWSHIP

The Lawrence Livermore National Laboratory (LLNL) has openings available under its Lawrence Fellowship Program. This is a highly desirable, prestigious postdoctoral position with ample resources and freedom to conduct cutting-edge research in a field of the candidate's choice. The duration of the Fellowship is up to three years. Typically two to four openings are available each year. Fellowships are awarded only to candidates with exceptional talent, credentials and a track record of research accomplishments.

Candidates will do original research in one or more aspects of science relevant to the mission and goals of LLNL which include: Physics, Applied Mathematics, Computer Science, Chemistry, Material Science, Engineering, Environmental Science, Atmospheric Science, Geology, Energy, Lasers and Biology. Successful candidates may participate in experimental or theoretical work at LLNL, and will have access to LLNL's extensive computing facilities, specialized laboratory facilities and field equipment. A senior scientist will serve as a mentor to each of the Fellows. The candidates will receive full management and administrative support. The salary is $7,933/mo.

Please refer to our web page **http://fellowship.llnl.gov** for eligibility requirements and application information. When applying and prompted, please mention where you saw this ad. The deadline for application is November 1, 2005. LLNL is operated by the University of California for the National Nuclear Security Administration/ Department of Energy. We are an Equal Opportunity Employer with a commitment to workforce diversity.

University of California
Lawrence Livermore
NATIONAL LABORATORY

http://jobs.llnl.gov

ASSISTANT PROFESSOR MOLECULAR BIOLOGY AND BIOCHEMISTRY RUTGERS UNIVERSITY

The Department of Molecular Biology and Biochemistry at Rutgers, The State University of New Jersey, New Brunswick (Busch Campus), invites applicants for a tenure-track **FACULTY POSITION**. The Department has a scientifically diverse faculty and is especially interested in applicants who use biochemical or molecular approaches in the areas of chromatin structure and function, genomic reprogramming, and control of growth and differentiation. The department is an important part of the expanding program in molecular biology within the Division of Life Sciences on the Busch campus, where the Center for Advanced Biotechnology and Medicine, the Waksman Institute and the Robert Wood Johnson Medical School are also located. We have strong consolidated, interdepartmental graduate programs in molecular biosciences. The position is highly competitive with regard to start-up funds, laboratory space and salary. Women and minority candidates are encouraged to apply. Please send by email to **nowakowski@biology.rutgers.edu** a curriculum vitae, list of publications, summary of research activities, a research plan, and arrange for three letters of recommendation to be sent by **December 1, 2005**, to: **Dr. Vincenzo Pirrotta, Chair, c/o Barbara Nowakowski, Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey, Nelson Biology Laboratories, 604 Allison Road, Piscataway, NJ 08854**.

Rutgers University is an Equal Opportunity/ Affirmative Action Employer.

DEPARTMENT HEAD
Neuroscience and Experimental Therapeutics
College of Medicine
The Texas A&M University System
Health Science Center

The Texas A&M University System Health Science Center College of Medicine, invites applications and nominations for the position of Head, Department of Neuroscience and Experimental Therapeutics. The Head will assume the leadership of a newly realigned department, and thus will have the opportunity to direct its development, including the recruitment of new faculty to build upon current research and teaching strengths within the Department and College. These include a flourishing multidisciplinary basic and clinical neurosciences group. New research space will become available in January 2006 on a competitive basis. In addition, commitment to a new research building is the number one legislative priority of the College and Health Science Center, presenting an exciting and unique opportunity for the new Head. The successful applicant should possess the following: (1) a doctorate in the Neurosciences or related fields and/or a MD degree; (2) an established record of exemplary research achievement; (3) a reputation for effective interpersonal and leadership skills; and (4) a strong commitment to excellence and innovation in medical education. The Head will guide and facilitate the continued development of programs/centers of excellence that will further enhance the national reputation of the Department and College. This necessarily includes fostering research collaborations within the College and its clinical academic partners, Scott & White Memorial Hospital & Clinic and the Central Texas Veterans Health Care System, as well as other components of the Health Science Center and The Texas A&M University System. Applications from female and minority candidates are strongly encouraged. Review of applications will begin as they are received.

Applicants should submit a current curriculum vitae and a statement of administrative philosophy, research goals and teaching interests, along with names and addresses of at least four references to: **Dr. Kelly Hester, Associate Dean for Academic Affairs, The Texas A&M University System College of Medicine, 164 Reynolds Medical Building, College Station, TX 77843-1114**. The College of Medicine's website is **http://medicine.tamhsc.edu**.

The Texas A&M University System Health Science Center is an Affirmative Action/Equal Opportunity Employer.

SLOAN-KETTERING INSTITUTE CELL BIOLOGY PROGRAM
Tenure-Track Faculty Positions

The Cell Biology Program, Sloan-Kettering Institute (www.ski.edu) has initiated a search for tenure-track faculty members. We are interested in outstanding individuals who have the potential to develop an innovative, independent research program that complements and enhances our existing strengths. Candidates with research interests in exciting areas of eukaryotic cell biology and using a variety of experimental approaches and systems are encouraged to apply. New faculty will be eligible for appointment in the recently established Gerstner Sloan-Kettering Graduate School of Biomedical Sciences as well as the Weill Graduate School of Medical Sciences of Cornell University. Sloan-Kettering has an outstanding infrastructure and state-of-the-art core resources. Construction of a new 21-story laboratory tower to be completed in early 2006 will allow significant expansion of our research programs.

Interested individuals should e-mail their CV, a description of past research accomplishments and proposed research, selected reprints and the names and contact details of three referees to: **cellbio@mskcc.org. Materials can also be submitted to Alan Hall, PhD, Chair, Cell Biology Program, c/o Stephanie Miranda, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 428, New York, NY, 10021.** Specific inquiries can also be made to **Dr. Hall or Ms. Miranda at cellbio@mskcc.org.** The application deadline is **November 17, 2005.** EOE/AA.

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.
www.mskcc.org

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

Scientific Review Administrator

The National Heart, Lung, and Blood Institute (NHLBI), a major research component of the National Institutes of Health (NIH), Department of Health and Human Services (DHHS), is seeking four Scientific Review Administrators for the Review Branch, Division of Extramural Affairs. Scientific Review Administrators organize and manage the comprehensive scientific and technical merit review of grant applications and contract proposals through interaction with established scientists in a variety of fields. Scientific Review Administrators are responsible for assuring the fairness and consistency of the review process, and for providing technical guidance to applicants, reviewers, and Institute staff.

Qualifications: Individuals with a Ph.D. or doctoral degree equivalent, and a scientific background in disciplines relevant to heart, lung, blood, or sleep disease research, are encouraged to apply. Experience in grant preparation and in the peer review process is desirable. For the basic qualification requirements, please refer to the NIH guidance for Health Scientist Administrators at **http://www.nhlbi.nih.gov/about/jobs/hsaguide.htm**. U.S. citizenship is required..

Salary: The current salary range is $62,886 to $114,882. In addition, a recruitment bonus may also be considered. Position requirements and detailed application procedures are provided on vacancy announcement NHLBI-05-94008, which can be obtained by accessing **WWW.USAJOBS.GOV**.

How to Apply: You may apply online at the above website or submit a Standard Form 171, Application for Federal Employment; OF-612, Optional Application for Federal Employment; current curriculum vitae/bibliography or other format to: **National Heart, Lung, and Blood Institute, Human Resources Branch G, Two Democracy Plaza, 6707 Democracy Blvd., Suite 700N, Bethesda, MD 20892**. All applications must be received by the October 7, 2005 closing date. For additional information contact **Chris Duggan** at **(301) 402-8028**.

DHHS and NIH are Equal Opportunity Employers. Applications from women, minorities and persons with disabilities is strongly encouraged. The NIH/NHLBI is a smoke free workplace.

COLUMBIA UNIVERSITY

Faculty Position in Biomedical Engineering

The Department of Biomedical Engineering in the Fu Foundation School of Engineering and Applied Science at Columbia University invites applications for a tenure-track faculty position at the Assistant, Associate, or Full Professor level. The candidate is expected to establish a strong research program in an area of biomedical engineering that can complement and enhance ongoing research in cellular and tissue engineering, biomechanics, and imaging. Of particular interest are candidates with expertise and research interest in one or more of the following relevant interdisciplinary areas, including functional tissue engineering, stem cells, advanced biomaterials and bioreactors, molecular or functional imaging, and biomechanics. The candidate should have a doctorate in Biomedical Engineering or a related discipline.

Applicants should send a complete curriculum vitae, three publication reprints, a statement of research and teaching interests, and names and contact information for four references to:

Professor Gordana Vunjak-Novakovic
Chair of the Faculty Search Committee
351 Engineering Terrace, MC 8904
1210 Amsterdam Avenue
Columbia University
New York, NY 10027

The search will remain open until the position has been filled.

Columbia University is an affirmative action/equal opportunity employer.
Women and minorities are encouraged to apply.

THE CITADEL
THE MILITARY COLLEGE OF SOUTH CAROLINA

Dean
School of Science & Mathematics

The Citadel invites nominations and applications for the position of Founding Dean of the School of Science and Mathematics and the Traubert Chair in Science and Mathematics. Candidates should possess an earned doctorate and have a strong commitment to promoting teaching and research at a predominantly undergraduate institution.

The Dean's primary responsibilities include general administration of the School and oversight of curricular, budgetary, academic program and faculty development matters. The School seeks a proven leader who will provide vision for both undergraduate and graduate programs. The successful candidate will be expected to facilitate and strengthen relations with alumni and the local community. The Dean is expected also to lead the School's fundraising and development efforts in close collaboration with the College's professional development staff.

The Citadel, The Military College of South Carolina, was founded in 1842 and is located in historic Charleston, South Carolina. It is a unique, coeducational state-assisted institution committed to educating principled leaders in a challenging intellectual environment. The School of Science and Mathematics offers both graduate and undergraduate degrees in Biology; Health, Exercise and Sport Science; and Mathematics and Computer Science and undergraduate degrees in Chemistry (ACS-accredited) and Physics. There are approximately 320 undergraduate and 75 graduate students in these programs. The School has 43 full-time faculty members actively engaged in teaching, research, and service.

Minimum qualifications:

- Earned doctorate in a basic sciences field or from one of the disciplines included in the School and demonstrated evidence of distinguished teaching, research, and significant scholarly work to qualify for appointment as a tenured full professor.
- A proven record of administrative experience in higher education that should include skills in planning, faculty development, budgeting and resource development.
- Strong interpersonal, communication, and decision-making abilities to interact effectively with the public and a commitment to excellence and diversity in the recruitment and retention of students, faculty, and staff.
- Commitment to shared governance and the values of educational excellence and service consistent with the mission and core values of The Citadel.
- Proven ability to:
  - Develop and maintain relationships with external constituencies
  - Acquire external resources through grants, contracts and gifts
  - Work effectively and collaboratively with the faculty at departmental and college levels
  - Foster teaching, research and professional development in a student-centered environment

Compensation is highly competitive and commensurate with education and experience. Applications should include a statement of educational and leadership philosophy; curriculum vita; a Citadel application (www.citadel.edu/hr); and the names, mailing, e-mail addresses, and telephone numbers of at least three references. Applications, inquiries and nominations should be directed to: Dr. Michael R. Ferrari, Senior Vice President and Managing Director, Higher Education Practice, EFL Associates, 2275 Half Day Road, Suite 350, Bannockburn, Illinois 60015. Phone: 847-821-2797. E-mail: mferrari@eflassociates.com. Please reference job #EA-02SCI. The review of nominations and applications will begin on November 15, 2005 and continue until an appointment is made (122649).

The Citadel is an affirmative action/ equal opportunity employer actively committed to ensuring diversity in all campus employment.

ScienceCareers.org

ScienceCareers.org

SCOTT & WHITE

College of Medicine
The Texas A&M University System
Health Science Center

Pediatric Hematology-Oncologist

The Section of Pediatric Hematology/Oncology at **Scott and White Clinic** and the **Texas A&M University System Health Science Center College of Medicine** (TAMUS HSC-COM) are seeking a clinician scientist with current research grants for a faculty position in a rapidly growing program. The candidate should be BE/BC in pediatric oncology and committed to an academic career. The successful candidates will join and enhance ongoing efforts in basic and translational research, with an institutional commitment to building a world-class experimental therapeutics program. An outstanding start-up package includes high quality laboratory space, excellent benefits and competitive salaries commensurate with academic qualifications. The position guarantees 75% protected time for research activities.

Scott & White Clinic is a 500+ physician directed multi-specialty group practice that is the leading provider of cancer care in Central Texas. Scott and White Clinic and the 486 bed tertiary Scott & White Memorial Hospital is the main clinical teaching facility for TAMUS HSC-COM. Outstanding clinical practice and laboratory facilities on campus that perform state of the art molecular and cellular biology research, flow cytometry, genomics and biostatistics are in place to support the research effort.

Please contact: **Don Wilson, M.D. Professor and Chairman, Department of Pediatrics, Scott & White, 2401 S. 31st, Temple, TX 76508. (800)725-3627 dwilson@swmail.sw.org Fax (254) 724-4974.**

For more information about Scott & White, please visit www.sw.org For Texas A&M www.tamhsc.edu. Scott & White is an equal opportunity employer.

Center for Immunology and Microbial Disease
Albany Medical College

Assistant/Associate Professor

The Center for Immunology and Microbial Disease at Albany Medical College invites applications for a tenure-track faculty position from individuals who have a doctoral degree, postdoctoral experience, and demonstrated research productivity. The successful candidate will be expected to establish an independent, extramurally funded research program and participate in the teaching of medical and graduate students. The basic science departments at Albany Medical College are organized as interdisciplinary research centers and the Center for Immunology and Microbial Disease has a focus on microbial pathogenesis and immune defense, particularly as related to biothreat agents and emerging infections. Faculty at the Albany Medical College receive competitive salaries, attractive start-up packages, and access to the Center's ABSL-3/BSL-3, Microbiology and Immunology Core Labs. In addition, we have established a close relationship with the New York State Department of Health Wadsworth Laboratories, providing a diverse environment that is rich in infectious disease expertise. Albany Medical College is located in a mid-sized city within the upstate New York Capital Region, and has easy access to Boston, New York City, and the Adirondack Mountains.

Applicants should send their curriculum vitae, a statement of research plans, and three letters of reference to:

Faculty Search Committee
Center for Immunology & Microbial Disease
Albany Medical College
47 New Scotland Avenue, MC-151
Albany, NY 12208

For further information about the Center, visit:
www.amc.edu/Academic/Research/imd.htm

An Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

ccri

CANCER SCIENTISTS

The **Children's Cancer Research Institute** (**CCRI**) of *The University of Texas Health Science Center at San Antonio* (UTHSCSA) is seeking outstanding candidates (Ph.D., M.D./Ph.D. or M.D.) for research or tenure-track positions at Assistant/Associate/Full Professor levels for its programs in molecular oncogenesis, hematologic malignancies, cancer genetics, and experimental cancer therapeutics. Applicants must have high quality peer-reviewed publications, evidence of independent research and competitive funding potential. The positions offer significant scientific resources and an attractive start-up support package.

The **CCRI** is a unique specialized cancer center, is housed in a new 100,000 sq. foot research facility on the North Campus of UTHSCSA and supported by a $200 million endowment from the tobacco settlement from the State of Texas [refer to http://ccri.uthscsa.edu]. Successful applicants will join a multidisciplinary team of researchers at the **CCRI**. The **CCRI** is a component of the UTHSCSA [refer to www.uthscsa.edu] which is located at the edge of the beautiful Texas Hill Country. San Antonio is the nation's eighth largest city and offers a rich, multi-cultural community with a thriving bioscience industry.

Review is ongoing and continues until positions are filled. Applicants should send current curriculum vitae, a description of research plans, and three letters of reference to:

Sharon B. Murphy, M.D.
Professor & Director

Children's Cancer Research Institute
The University of Texas Health Science Center at San Antonio

MC 7784
7703 Floyd Curl Drive
San Antonio, TX 78229-3900
[210] 562-9003 or murphysb@uthscsa.edu

All faculty appointments are designated as security sensitive positions.
UTHSCSA is an Equal Employment Opportunity/Affirmative Action Employer.

POSTDOCTORAL FELLOWSHIP OPPORTUNITIES

The **Santa Fe Institute** (SFI) anticipates several openings for postdoctoral fellowships beginning in September 2006.

SFI research is devoted to complex phenomena drawing input from a wide variety of fields, including biology (e.g., genomics, evolution, ecology, immunology, biochemistry & cellular organization, systems & bioinformatics, structure of non-human social groups), computer science (computational complexity, adaptive & resilient computation, novel forms of computation, simulation), physics and mathematics (nonlinear systems, statistical physics, biophysics), and the sciences of human behavior (cognition, neuropsychological development, cultural evolution, market structure & function, evolution of human language). Applications are also welcome from disciplines other than those listed here.

SFI research is integrative, and there are no formal programs or departments. Postdoctoral Fellows have the opportunity to work either on existing research projects or projects of their own initiation. Research at the Institute focuses primarily on mathematical and computational approaches, although applicants whose research will include an experimental or data-collection component in collaboration with off-site colleagues are also encouraged to apply. Further details about SFI's current research can be found at http://www.santafe.edu/indexResearch.php. Postdoctoral Fellows are appointed for two-year terms on a full-time basis, with the possibility of a one-year extension contingent on funding and performance.

Candidates should have a Ph.D. (or expect to receive one before September 2006), with an academic record of scientific excellence, an ability for independent research, and a strong interest in interdisciplinary approaches and collaboration.

Applications are welcome from candidates in any country. Women and minorities are especially encouraged to apply. Successful foreign applicants must acquire an acceptable visa (usually a J-1) as a condition of employment.

TO APPLY: Please view the full position announcement and application instructions at http://www.santafe.edu/postdoc06.html. For full consideration, all application materials must be received electronically (preferred) or via post no later than **November 15, 2005**. For further information, e-mail postdocinfo@santafe.edu or call (505) 946-2746.

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COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Neuroscience Faculty Recruitment

A new Neuroscience Initiative at Columbia University is recruiting faculty with interests in the analysis of neural circuitry through molecular, genetic, cellular electrophysiological and/or imaging approaches. We are particularly keen to attract individuals whose research program explores neural circuits in genetically tractable model systems and in the context of well-defined behaviors. We encourage applications for positions at the Assistant Professor level, but will also consider applications from more senior investigators for positions at the level of Associate or full Professor.

Columbia University currently has a world-renowned program in neurobiology and behavior and the new Neuroscience Initiative aims to enhance interactions between basic and clinical neurosciences, and link the neurosciences to other scientific disciplines within the University. Faculty will be affiliated with the Center for Neurobiology and Behavior, and there will be opportunities for strong ties with scientific departments and programs on the Morningside Heights campus.

Applications for this round of recruitment are requested by November 18, 2005. A C.V., cover letter including statement of interests, and three letters of reference under separate cover should be emailed care of **Dr. Sarah Caddick, dgl2102@columbia.edu.** In addition, please mail a hard copy of these documents to:

Chair, Neuroscience Search Committee
c/o Dr. Sarah Caddick
Columbia University
Hammer Health Sciences Center
Room 2-205G
701 West 168th Street
New York NY 10032

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Cornell University
Center for Vertebrate Genomics

Postdoctoral Positions in Vertebrate Genomics

Cornell University, situated in scenic upstate New York, has several postdoctoral positions available with faculty in the Center for Vertebrate Genomics (CVG), dedicated to promoting research and education in vertebrate genetics and functional genomics throughout Cornell University. The CVG offers resources and opportunities for participating postdocs, including travel funds, teaching opportunities, research support, an active genomics club, an annual symposium, and postdoctoral fellowships. Faculty with open positions are listed below:

- **Andrew Clark (ac347@cornell.edu)**, Comparative genomics; association testing.
- **Ted Clark (tgc3@cornell.edu)**, Zebrafish immune function.
- **Tim DeVoogd (tjd5@cornell.edu)**, Comparative avian brain development.
- **W. Lee Kraus (wlk5@cornell.edu)**, Genomic analysis of signal-regulated transcription in humans.
- **David Lin (DML45@cornell.edu)**, Development of the olfactory system.
- **Dan Luo (DL79@cornell.edu)**, Nanobiotechnology.
- **Vicki Meyers-Wallen (vnm1@cornell.edu)**, Canine development and inherited disease.
- **Alexander Nikitin (an58@cornell.edu)**, Mouse Models of Cancer.
- **Tim O'Brien (tpo5@cornell.edu)**, Mouse Developmental Genetics.
- **Mark S. Roberson (msr14@cornell.edu)**, Molecular endocrinology and reproduction.
- **John Schimenti (jcs92@cornell.edu),** Mouse Genetics.
- **Robert Weiss (rsw26@cornell.edu)**, Genome Maintenance Mechanisms.

For more information about the CVG and faculty research programs, visit www.vertebrategenomics.cornell.edu. Applications, including a CV and contact information for three references, should be sent by email directly to individual faculty.

Cornell University is an Affirmative Action/Equal Opportunity Employer and Educator.

Memorial Hermann Healthcare System's new comprehensive, independent clinical research institute has an excellent opportunity for an Executive Director. Located within Memorial Hermann Hospital in Houston's world-renowned Texas Medical Center, this institute will facilitate quality, safe, efficient and cost-effective research in a variety of areas, including cardiovascular diseases, neurosciences, trauma, orthopedics, anesthesiology, oncology and others.

EXECUTIVE DIRECTOR OF CLINICAL RESEARCH INSTITUTE

The selected candidate will report to the Vice President and CFO, providing leadership and vision for the institute, as well as ensuring scientific validity, financial strength and operational efficiency. Requirements include an MD or PhD with 10 years clinical research experience in a university or teaching hospital and 5 years in management role. Must also have extensive knowledge of federal regulations regarding research administration.

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FOUNDING DIRECTOR
SCHOOL OF EARTH AND SPACE EXPLORATION
ARIZONA STATE UNIVERSITY

Arizona State University announces a nationwide search to recruit a Founding Director for its new School of Earth and Space Exploration (SESE). This new school integrates across the earth sciences, planetary sciences, astrophysics, and engineering. SESE is designed to position Arizona State University as a national leader in the coming decades in the exploration of our world, solar system, and universe, and to provide world-class educational experiences for the University's undergraduate and graduate students. This new school has two main goals: (1) to accelerate the pace of discovery by eliminating barriers between traditional scientific disciplines and by integrating systems engineering with the sciences, and (2) to train a new type of transdisciplinary explorer – scientists with experience in engineering and engineers with a strong understanding of science.

Reporting to the Vice President and Dean of the College of Liberal Arts and Sciences, the Founding Director is expected to: provide visionary and entrepreneurial leadership for the full range of activities within the School; oversee significant growth in the School's faculty and research programs; oversee the development of the graduate and undergraduate programs; and maintain a productive research program. The successful candidate must possess an earned doctorate in a discipline relevant to the School and have an established record of academic or professional achievement appropriate to the rank of Professor. Owing to the transdisciplinary nature of SESE's curriculum and research, the Founding Director must be familiar with the fundamental precepts of science and engineering. The Founding Director will spend significant time generating new external resources and funding opportunities for SESE faculty, and must be familiar with the federal budget process and the strategic goals of the funding agencies. Experience with research program development, experience with overseeing large programs or organizations related to the mission of SESE, and evidence of excellent communication, interpersonal, and organizational skills are highly desired.

Salary and start-up will be competitive and commensurate with qualifications. Applicants must submit a cover letter and current Curriculum Vitae via mail, fax, or email (in MS Word or pdf format). Applications and nominations will be accepted until the Director is selected, but interested parties are encouraged to submit their resumes and nominations by **October 31, 2005** to assure optimal consideration. ASU requires a background check prior to official hire. ASU has retained R. William (Bill) Funk, National Managing Director of the Education Practice at Korn/Ferry International, to assist in this search effort and all candidate correspondence should be sent to him as follows:

R. William (Bill) Funk
2100 McKinney Avenue, Suite 1800
Dallas, Texas 75201
Email: allegro.feito@kornferry.com
Fax: 214/954-4370

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FACULTY POSITION
BEHAVIORAL MOLECULAR ECOLOGY
Cornell University

The Department of Neurobiology and Behavior at Cornell University is seeking a faculty member (Assistant Professor preferred, but candidates for Associate or Full Professor will be considered) doing innovative work on interactions among animals, plants, or microbes. Topics of interest include, but are not limited to, attractive or defensive interactions, chemical signaling/communication, and adaptive responses of organisms to their social environments. We especially seek scientists who explore novel areas of behavioral ecology with a significant molecular (chemical or genetic) component to their research. The successful applicant will become a member of the Department of Neurobiology and Behavior (NBB) and will join the university program in Molecular and Chemical Ecology, which already includes faculty in the Departments of NBB and Ecology and Evolutionary Biology, and in the Boyce Thompson Institute for Plant Research. He/she will be expected to contribute to the graduate and undergraduate teaching mission of the Department of NBB. This is a tenure-track position with 50% research and 50% teaching responsibilities.

Review of applications will begin **November 4, 2005**. To apply, send a curriculum vitae, description of research accomplishments and plans, a statement of teaching interests, and three letters of reference to: **Professor Kern Reeve, Chair, Search Committee, Department of Neurobiology and Behavior, Seeley G. Mudd Hall, Cornell University, Ithaca, NY 14853 (phone 607/254-4340; fax: 607/254-1303; e-mail: tmn3@cornell.edu).**

WAYNE STATE UNIVERSITY
BIOLOGICAL CHEMISTRY FACULTY POSITION

The Department of Chemistry at Wayne State University seeks applications for a tenure-track position in the Division of Biological Chemistry at the assistant professor level. Candidates must have a Ph.D. and the potential to develop a nationally recognized, externally funded research program of outstanding quality in an area of biological chemistry. The Department offers exciting opportunities for candidates with research interests complementing a large group of faculty working in the areas of DNA, RNA and protein biochemistry, enzymology, carcinogenesis, biophysical, bioorganic, and bioinorganic chemistry, as well as molecular and cellular biology (see departmental website **http://chem.wayne.edu** for further information).

The Department of Chemistry has a supportive academic environment and a strong graduate program. Excellent opportunities exist for collaborative research with individuals in the Department of Biological Sciences, the basic science departments in the highly ranked School of Medicine, the College of Pharmacy and Health Sciences, as well as in the Center for Molecular Medicine and Genetics, the Institute for Environmental Health Sciences, and the Barbara Ann Karmanos Cancer Institute. The Department of Chemistry offers an excellent research environment that includes ample, newly renovated research laboratories and a fully staffed Central Instrument Facility that manages research-level ESI MS, MALDI TOF, EPR, TEM, and NMR instrumentation (including a 700 MHz NMR with cryoprobe). The Wayne State Faculty also have access to the resources of the Michigan Core Technology Alliance (**http://www.ctaalliance.org/**), which includes facilities for bioinformatics, proteomics, genomics, animal models and structural biology, including 900 MHz NMR and a dedicated synchrotron beamline for X-ray crystallography.

Applicants should submit a complete resume and description of future research plans, as well as three letters of recommendation addressing both research and teaching potential. All materials should be sent to: **Professor Charles H. Winter, Associate Chair, 141 Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, MI 48202-3489**. Review of applications will begin in **October 2005**.

Women and minority candidates are encouraged to apply.
Wayne State University is an Equal Opportunity and Affirmative Action Employer.

POSITIONS OPEN

ENVIRONMENTAL MICROBIOLOGIST

Applications are invited to fill a tenure-track position in Kent State's Department of Biological Sciences (**website: http://www.kent.edu/biology**) at the level of **ASSISTANT PROFESSOR.** This position is part of an ongoing expansion of the faculty in biological sciences. We seek a research-focused microbiologist able to apply modern molecular techniques to the study of environmental microbiology. Individuals must have a strong commitment to collaborative and interdisciplinary research. The successful candidate is expected to establish a high-quality, extramurally funded research program and exhibit a commitment to excellence in graduate and undergraduate education. Applicants must have a Ph.D. degree in microbiology, biology or a related discipline, and postdoctoral experience. The University provides superb core research facilities, field research sites, and a competitive startup package.

Applicants should send curriculum vitae and relevant reprints, a statement of research and teaching interests including plans for future research, and three letters of recommendation. Materials should be sent to:

Chair, Environmental Microbiologist Search Committee
Department of Biological Sciences
Kent State University
P.O. Box 5190
Kent, Ohio 44242-0001
Fax: 330-672-3713

Review of applications will begin October 20, 2005, and continue until the position is filled. *Kent State University is an Affirmative Action/Equal Opportunity Employer and encourages applications from candidates who would enhance the diversity of the University's faculty.*

FACULTY POSITION IN CHEMISTRY (Position #821)
University of California, Berkeley
Department of Chemistry

The Department of Chemistry at the University of California, Berkeley solicits applications for a faculty position beginning in fall 2006. Outstanding senior-level and junior-level applicants will be considered. Creative and energetic candidates who show extraordinary promise or accomplishment in research and teaching are specifically sought in the field of bioorganic chemistry; however, exceptional candidates in any area of chemistry will be considered. Junior-level applicants should send curriculum vitae and a proposed research program, and arrange to have three letters of recommendation sent to: **Chair, Faculty Recruitment Committee; Department of Chemistry; University of California; Berkeley, CA 94720-1460.** Please refer references to the University of California statement on confidentiality at **website: http://www.chance.berkeley.edu/apo/evalltr.htm.** The deadline for receipt of applications is November 15, 2005. Application review will begin with receipt of applications. *The University of California is an Equal Opportunity/Affirmative Action Employer.*

ASSISTANT PROFESSOR OF BIOLOGY
Developmental or Invertebrate Biology

Saint Vincent College invites applications for a tenure-track position beginning fall 2006. Requirements include Ph.D., commitment to undergraduate education, and broad training in developmental biology or invertebrate zoology. Postdoctoral or teaching experience preferred. Teaching responsibilities include general biology, upper level cell biology, upper level course in developmental or invertebrate biology, course for nonscience majors, and supervision of senior research projects. Send letter of application, curriculum vitae, three letters of recommendation, graduate and undergraduate transcripts, statements of teaching philosophy, and research interests by October 28, 2005, to: **Director of Human Resources, Saint Vincent College, 300 Fraser Purchase Road, Latrobe, PA 15650-2690.** For more information, go to **website: http://www.stvincent.edu/hr2.** *Equal Opportunity Employer.*

POSITIONS OPEN

USC UNIVERSITY OF SOUTHERN CALIFORNIA

ASSISTANT/ASSOCIATE PROFESSOR
Genetics/Inflammation/Cell and Developmental Biology

The University of Southern California Institute for Genetic Medicine (IGM) has an immediate opening for a tenure-track Assistant or Associate Professor to conduct cutting-edge basic research in cellular and molecular biology and/or human and molecular genetics. The successful candidate will establish an independent research program with relevance to wound healing, broadly interpreted. Examples are skin biology, tissue microenvironments, inflammation, angiogenesis, tissue engineering, stem cells, and model organisms. The successful candidate will work within the vibrant research environment of the IGM and interface with an established translational research program in wound healing within the Department of Surgery. Competitive salary and startup package and participation in graduate training are available for a broadly trained Ph.D. or M.D./Ph.D. to establish a research program within the IGM (**website: http://www.usc.edu/igm**).

Applications should include resume, research statement, future plans, and three letters of reference addressed to: **Dr. Larry Kedes, Director of the Institute for Genetic Medicine.** Candidates for Associate Professor need not arrange for letters of reference at this time. Submission of applications and letters of reference by e-mail is preferred (Microsoft Word or PDF). Send applications to **e-mail: igm@usc.edu** with Subject header IGM/Wound Healing Search or to: **IGM/Wound Healing Search Committee, Institute for Genetic Medicine, University of Southern California, 2250 Alcazar Street CSC/IGM-240, Los Angeles, CA 90033.** All materials must be received by January 15, 2006. *Keck School of Medicine, University of Southern California is an Equal Opportunity Employer.*

The Vanderbilt Institute of Chemical Biology (VICB) and the **Vanderbilt University School of Medicine** are seeking applicants for a tenure-track **FACULTY POSITION** at any level. Vanderbilt has outstanding infrastructure in high throughput screening, mass spectrometry, proteomics, nuclear magnetic resonance, antibody generation, chemical synthesis, and imaging that complement world-class, disease-based research centers. This provides a rich environment for individuals interested in developing novel therapeutic, diagnostic, or imaging strategies. Academic appointments will be made in an appropriate Department of the School of Medicine. Senior applicants should submit curriculum vitae and junior applicants should submit curriculum vitae, a summary of research interests, and three letters of recommendation to: **Lawrence J. Marnett, Vanderbilt Institute of Chemical Biology, Vanderbilt University School of Medicine, Nashville, TN 37232.** Submit by **e-mail: vicb@vanderbilt.edu.** For more information about the VICB see **website: http://www.vanderbilt.edu/vicb.** *Vanderbilt University is an Equal Employment Opportunity/Affirmative Action Employer.*

EXECUTIVE DIRECTOR

The Valles Caldera Trust, a wholly owned government corporation, seeks an Executive Director to administer the 89,000-acre Valles Caldera National Preserve. The ideal candidate will have demonstrated leadership experience, operational and financial acumen, a successful history of advocacy and outreach interfacing with diverse constituencies, and the ability to raise funds through charitable contributions and grants. For a position description and contact information, go to our **website: www.vallescaldera.gov.** For additional information, contact: **Barbara Johnson** at **e-mail: lunah3@comcast.net or phone: 505-474-6689.** Applications must be received by November 15, 2005. *The Valles Caldera Trust is an Equal Opportunity Employer.*

POSITIONS OPEN

ECOSYSTEM/WATERSHED ECOLOGIST

Applications are invited to fill a tenure-track position in Kent State's Department of Biological Sciences (**website: http://www.kent.edu/biology**) at the level of **ASSISTANT PROFESSOR.** This position is part of an ongoing expansion of the faculty in biological sciences. Applicants studying interactions between aquatic and terrestrial ecosystems that complement our strong aquatic ecology program are particularly encouraged to apply. Departmental strengths include on-campus research wetlands, superb core research facilities, diverse field sites, and competitive startup packages. The successful candidate is expected to establish a high-quality, extramurally funded research program and exhibit a commitment to excellence in graduate and undergraduate education. Applicants must have a Ph.D. degree in ecology, biology or a related discipline, and postdoctoral experience.

Applicants should send curriculum vitae and relevant reprints, statement of research and teaching interests including plans for future research, and three letters of recommendation. Materials should be sent to:

Chair, Ecosystems Ecology Search Committee
Department of Biological Sciences
Kent State University
P.O. Box 5190
Kent, Ohio 44242-0001
Fax: 330-672-3713

Review of applications will begin October 20, 2005, and continue until the position is filled. *Kent State University is an Affirmative Action/Equal Opportunity Employer and encourages applications from candidates who would enhance the diversity of the University's faculty.*

TENURE-TRACK POSITION IN VECTOR-BORNE DISEASES AND MOLECULAR ENTOMOLOGY

The Department of Biochemistry at Virginia Tech (**website: http://www.biochem.vt.edu/**) seeks applicants for an open-rank assistant/associate tenure-track assistant professor position in vector-borne diseases and molecular entomology. The successful candidate will join current faculty including four recent hires in vector-borne disease research and will be a member of the newly formed Institute of Biomedical and Public Health Sciences (IBPHS) (**website: http://www.ibphs.vt.edu**). Preference will be given to candidates who utilize genomics, bioinformatics, proteomics, and molecular approaches to study vector-pathogen interactions and the biology of human or animal disease vectors. The successful candidate will build and maintain an internationally recognized, extramurally funded research program, will participate in instruction, and will be open to collaborative research. Competitive startup packages for equipment and for technical and graduate student support will be provided. Applicants should apply online (**website: http://www.jobs.vt.edu,** use posting number 041106) and arrange for three reference letters to be sent to: **Chair, Vector-Borne Disease Search Committee, Dr. Jake Tu, Department of Biochemistry, Virginia Tech, Blacksburg, VA 24061. E-mail: jaketu@vt.edu; telephone: 540-231-8062.** Applications will be reviewed beginning December 1, 2005. However, the position remains open until filled. *Virginia Tech is an Equal Opportunity/Affirmative Action Institution.*

The University at Albany – State University of New York seeks a Biological Anthropologist (**ASSISTANT PROFESSOR**). Research focus should complement existing strengths. Ability to develop an externally funded research program expected. Participation in an interdisciplinary human biology major and programs in a four-field Anthropology Department required. Deadline is November 7, 2005. For more details, go to **websites: http://www.albany.edu/anthro/bioanthjob.htm** and **http://hr.albany.edu/content/vacancy.asp.**

Assistant Professor – Molecular Oncology Endowed Chair – Moffitt Cancer Center & Research Institute

The University of South Florida (USF) College of Medicine's Department of Interdisciplinary Oncology and the H. Lee Moffitt Cancer Center & Research Institute, an NCI-designated Comprehensive Cancer Center, are seeking a distinguished scientist for a Professorship position in the Molecular Oncology Program. In addition to the academic appointment at USF, this position is also an Endowed Chair at the Moffitt Cancer Center.

The successful candidate must possess a Ph.D. or M.D. degree and an excellent track record of independent research as demonstrated by high quality publications in peer-reviewed journals and sustained extramural funding. The candidate must also have at least five years academic experience at the Associate Professor rank. Preference will be given to individuals who will complement current existing interests in our program including, but not limited to, the broad areas of gene regulation, signal transduction, cancer genetics and functional genomics. However, outstanding candidates from all other research areas will be considered. The position is tenure earning and salary is negotiable.

Please reference position no. DIO0524. Interested candidates should send curriculum vitae and a brief statement of major academic interests in one single pdf document to the Molecular Oncology Search Committee at koransky@moffitt.usf.edu. Application review begins November 15, 2005. The position is open until filled.

H.LEE MOFFITT Cancer Center & Research Institute

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USF University of South Florida College of Medicine

The University of South Florida is an EO/AA/EA institution. For disability accommodations, contact Kathy Jordan (813-632-1451) a minimum of five working days in advance. According to Florida law, applications and meetings regarding them are open to the public.

www.moffitt.usf.edu

Learn more

Executive Director, Wisconsin Institute for Biomedical and Health Technologies

The University of Wisconsin-Milwaukee is in the process of launching an institute and invites nominations and applications for the position of Executive Director for the Wisconsin Institute for Biomedical and Health Technologies (WIBHT). UW-Milwaukee is a doctoral research-extensive university in the 26-campus University of Wisconsin System. With an annual operating budget of about $465 million, the University offers 83 undergraduate majors, 48 master's degrees, and 20 doctoral programs, serving over 27,000 students. The 92-acre main campus is located in a residential neighborhood near the shores of Lake Michigan, just minutes from downtown Milwaukee.

The Executive Director will lead one of the University's top strategic initiatives. WIBHT, a new multi-institutional interdisciplinary initiative with approved initial funding, is intended to leverage the biomedical and health innovations capabilities of Southeastern Wisconsin. The participating schools and colleges include the College of Engineering and Applied Science, the College of Letters & Science, the College of Health Sciences, the College of Nursing, the School of Business Administration, and the Medical College of Wisconsin. Corporate partners have already made significant commitments to WIBHT.

The Executive Director will be responsible for establishing the initiative in collaboration with existing interdisciplinary teams, and institutional and corporate partners. Initial activities are expected to focus on medical imaging and health informatics technologies. The Executive Director will be fully responsible for the management of WIBHT's activities. Reporting to a Governing Board, the Executive Director will formulate strategic plans, work to secure extramural funding, and establish collaborations with academia, government, and industry. The Executive Director will also coordinate interaction with the UW System's Wisys and WARF intellectual property commercialization operations.

The ideal candidate will possess interdisciplinary breadth, outstanding communication and management skills, and a demonstrated track record of substantial extramural funding in pursuit of scholarly activities. Familiarity with technology transfer and the commercialization cycle is preferred. A Ph.D. and an established distinguished scholarly record in biomedical imaging or health informatics are required.

The Executive Director must be eligible for a tenured faculty appointment as full professor in an appropriate college and department. A competitive start-up package will be provided. The campus has also committed funding for a team of three to four researchers. Substantial additional funding is available for ongoing programs subject to reaching agreed milestones.

Application Procedure: Interested candidates should submit a letter of application, curriculum vitae and the names and contact information for five references. Screening will begin Oct. 30, 2005, and continue until the position is filled. Applicants and nominators are strongly encouraged to submit their materials by email as attachments. Submit nominations and applications to:

Denise Newell
Office of the Provost
215 Chapman Hall
2310 E. Hartford Ave.
University of Wisconsin-Milwaukee
Milwaukee, WI 53201
E-mail (preferred): neweld@uwm.edu

Questions about the position may be directed to Dean Sally Lundeen, Chair of the Search Committee, at **slundeen@uwm.edu** or (414) 229-4189.

For more information about WIBHT, please visit **http://www.uwm.edu/News/report/05.06/R_JUN05.pdf**. To learn more about the University of Wisconsin-Milwaukee, please visit **www.uwm.edu**.

For the campus security report, see **http://www.cleryact.uwm.edu**, or call the Office of Student Life, Mellencamp Hall 118 at (414) 229-4632 for a paper copy.

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POSITIONS OPEN

DEAN, SCHOOL OF SCIENCE

Saint Mary's College of California seeks a leader who will build upon a record of success and lead the School of Science to its next level of academic excellence. With strong institutional support, the Dean will continue to develop our outstanding undergraduate science and mathematics programs and our national reputation as a leader in undergraduate science education.

The Dean, as the primary academic advocate and administrative officer of the School, promotes the vitality, integrity, and advancement of all programs and ensures that the programs and the policies of the School are consistent with the College's mission.

The School has a full-time faculty of nearly 50, representing the disciplines of biology, chemistry, computer science, mathematics, physics, psychology, environmental science, and three-plus-two engineering, as well as a consortium arrangement with Samuel Merritt College of Nursing. The faculty is committed to teaching effectiveness and scholarly research; providing our students with outstanding educational experiences; vibrant and innovative teaching; personal contact between professor and student; collaborative research projects that convey the excitement and hands-on nature of all scientific investigations.

Earned doctorate in an appropriate field; distinguished record of teaching, service, and scholarship commensurate with rank of full Professor.

Deadline: Review for the position begins October 15, 2005. The position is opened until filled.

To apply: A complete application includes a letter of application, a current curriculum vitae, the names and contact information of five references, and any other materials the applicant deems relevant. Send to:

Frances Sweeney, Ph.D.
Vice Provost of Academic Affairs
Saint Mary's College of California
P.O. Box 4228
Moraga, CA 94575-4228
Website: http://www.stmarys-ca.edu

An independent institution, Saint Mary's draws upon three principal traditions: the liberal arts, Catholicism, and the LaSallian education vision of Saint John Baptist DeLaSalle.

Saint Mary's College of California is an Equal Opportunity Employer, committed to diversity and encourages Christian Brothers, women, minorities, persons with disabilities, and veterans to apply. The College seeks faculty, staff, and administrators who espouse or respect the Catholic tradition.

ANIMAL PHYSIOLOGY POSITION

The Department of Biology at the University of North Dakota seeks an animal physiologist for a tenure-track position as an **ASSISTANT PROFESSOR,** or **ASSOCIATE PROFESSOR** in the case of an appropriately qualified candidate. The Department offers graduate degrees through the Ph.D. and provides an environment conducive for building a competitive research program. The successful candidate will be expected to establish a productive and extramurally funded research program. A Ph.D. is required; postdoctoral experience is desirable. Teaching duties include an undergraduate lecture/laboratory course in animal physiology, and potential participation in an introductory biology course. Development of an additional upper level or graduate course in the area of specialty will be expected in the future. Teaching expectations for junior candidates will not exceed two courses per year during the first several years. The position will begin 16 August 2006. Review of applications will begin 1 November 2005 and will continue until the position is filled. Send curriculum vitae, three representative reprints, statements of teaching and research interests, and have three letters of reference sent directly to:

Dr. Richard Crawford
Department of Biology
Box 9019
University of North Dakota
Grand Forks, ND 58202-9019

For more information see **website: http://www.und.edu/dept/biology/jobs.htm.** *The University of North Dakota is an Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

Colorado
University of Colorado at Boulder

FACULTY POSITION IN MOLECULAR, CELLULAR AND DEVELOPMENTAL BIOLOGY

The Department of Molecular, Cellular, and Developmental (MCD) Biology invites applications for a tenure-track **ASSISTANT PROFESSOR** in the area of molecular, cellular, or developmental biology.

Applicants must have a Ph.D., M.D., or equivalent and postdoctoral research experience. The candidate is expected to develop a vigorous and innovative research program and have enthusiasm for teaching at the undergraduate and graduate levels. Applicants should submit curriculum vitae and a concise statement of research and teaching interests and should arrange to have three reference letters sent to:

MCDB Faculty Search Committee
Department of MCD Biology
University of Colorado at Boulder
347 UCB
Boulder, CO 80309-0347

Review of applications will begin December 1, 2005. Applications will continue to be accepted until the position is filled. *The University of Colorado at Boulder is committed to Diversity and Equality in Education and Employment.*

NEUROSCIENCE

Applications are invited to fill a tenure-track position in Kent State's Department of Biological Sciences (**website: http://www.kent.edu/biology**) at the level of **ASSISTANT PROFESSOR** beginning in August 2006. This position is part of an ongoing expansion of the faculty in biological sciences. Departmental strengths include programs in neurobiology, physiology, and molecular biology, superb core research facilities, and competitive startup packages. Research in all areas of neuroscience will be considered. The successful candidate is expected to establish an extramurally funded research program and exhibit a commitment to excellence in graduate and undergraduate education. Applicants must have Ph.D. degree in a related discipline and postdoctoral experience.

Applicants should send curriculum vitae, statements of research and teaching interests, and three letters of recommendation to:

Chair, Neuroscience Search Committee
Department of Biological Sciences
Kent State University
P.O. Box 5190
Kent, OH 44242-0001
Fax: 330-672-3713

Review of applications will begin October 20, 2005, and continue until the position is filled.

Kent State University is an Affirmative Action/Equal Opportunity Employer and encourages applications from candidates who would enhance the diversity of the University's faculty.

CELL/MOLECULAR/DEVELOPMENTAL BIOLOGIST

The Department of Biological Sciences at Marquette University has a tenure-track **ASSISTANT PROFESSOR** position available August 16, 2006, for a biologist to join a faculty with broad research interests (**website: http://biology.marquette.edu**). Applicants must have a Ph.D. with postdoctoral experience. The successful candidate is expected to develop an extramurally funded research program. Teaching responsibilities include an annual undergraduate lecture course in animal development in the spring semester and a graduate lecture or seminar course in the candidate's area of expertise in the fall semester. Send curriculum vitae, statement of research interests, and three letters of reference by November 15, 2005 to: **Dr. Robert Fitts, Chair, Department of Biological Sciences, WLS 112, P.O. Box 1881, Milwaukee, WI 53201-1881.**

POSITIONS OPEN

ASSISTANT OR ASSOCIATE PROFESSOR IN COMPARATIVE IMMUNOLOGY

University of Alberta
Department of Biological Sciences

We invite applications for a tenure-track position at the Assistant or Associate Professor level in research areas related to comparative immunology (nonstandard model organisms, including invertebrates). The successful candidate will interact with a dynamic immunology and infection group as well as colleagues with expertise in developmental, molecular and evolutionary biology. The candidate should have a strong record of research and have the potential for excellence in teaching within our successful Immunology and Infection program. The candidate must have a Ph.D. and two or more years of postdoctoral research experience.

The University of Alberta offers a competitive salary commensurate with experience and an excellent benefits plan. The Department of Biological Sciences (**website: http://www.biology.ualberta.ca/**), with 70 faculty members and 275 graduate students, offers an exciting environment for collaborative research. Exceptional infrastructure includes molecular biology and advanced microscopy and imaging service units and aquatic and terrestrial animal care facilities.

Candidates should submit curriculum vitae, a one-page summary of research plans, a statement of teaching interests, and reprints of their three most significant publications electronically to **e-mail: positions@biology.ualberta.ca** or by mail to:

Dr. L. S. Frost, Chair
Department of Biological Sciences
CW 405 Biological Sciences Building
University of Alberta
Edmonton, Alberta, Canada T6G 2E9

Applicants must also arrange for three confidential letters of reference to be sent to the Chair. Closing Date: November 15, 2005. The effective date of employment will be July 1, 2006.

All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. The University of Alberta hires on the basis of merit. We are committed to the principle of equity in employment. We welcome diversity and encourage applications from all qualified women and men, including persons with disabilities, members of visible minorities, and Aboriginal persons.

ASSISTANT PROFESSOR/CURATOR ORGANISMAL BIOLOGIST

The Bell Museum of Natural History at the University of Minnesota announces a nine-month tenure-track position for an Assistant Professor and museum Curator (**website: http://www.bellmuseum.org/curator.html**). The successful candidate will have an active, specimen-based research program involving amphibians, reptiles, or noninsect invertebrates, emphasizing a conceptual focus such as biodiversity, biogeography, coevolution, comparative biology, conservation, evolution-development, paleontology, phylogenetics, population processes, or other related topical areas. In addition to maintaining an innovative, extramurally funded research program, the successful candidate will be expected to contribute to the education mission of the University, curate either the amphibian and reptile or invertebrate collection, and help maintain scientific content and accuracy in the museum's outreach programs. A Ph.D. is required and postdoctoral experience is preferred. Bell Museum curators hold tenure in a variety of academic departments across the University and the tenure-home for this position will be determined based on the research focus and potential curricular contributions of the successful applicant. Please send curriculum vitae; up to five selected reprints; statements of research, teaching, and curatorial interests; and names and full contact information of three references to: **Search Committee, Bell Museum of Natural History, 10 Church Street S.E., University of Minnesota, Minneapolis, MN 55455-0104.** Applications will be considered beginning 11 November 2005. *The University of Minnesota is an Equal Opportunity Educator and Employer.*

ScienceCareers.org

Postdoctoral Position in Psychology or Psychiatry

Mood and Anxiety Disorders Research Program

National Institute of Mental Health
Bethesda, MD

The Section of Developmental Genetic Epidemiology in the Mood and Anxiety Disorders Program at the National Institute of Mental Health is recruiting a postdoctoral fellow in experimental psychology, biological psychology/psychiatry, clinical psychology, neuro-psychology/psychiatry, or related field. The focus of the section is genetic epidemiologic and community studies, particularly family and high-risk studies of the correlates and risk factors for the development of mood and anxiety disorders. The candidate must have a Ph.D. in psychology or a M.D. with psychiatry residency, and some research experience is preferred. Preference will be given to candidates with a background and interest in the fundamentals of stress, the autonomic nervous system, and/or reproductive endocrinology/hormones. Applicants should send a curriculum vitae, statement of research interests, and three letters of reference to Dr. Kathleen R. Merikangas, Chair Search Committee, National Institute of Mental Health, 35 Convent Drive, Bldg 35 Room 1A201, MSC-2370, Bethesda, MD 20892-3720.

DHHS and NIH are Equal Opportunity Employers

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

The Institute of Isotope Geology and Mineral Resources has several

Postdoctoral Research Positions in Isotope Geochemistry

available to be filled.

Requirements: The successful candidates will be expected to conduct their own research and strongly interact within the Isotope Geochemistry Group. Applicants should hold a Ph.D. in geochemistry/cosmochemistry and should have demonstrated outstanding expertise in some of the following areas: mass spectrometry, analytical chemistry, geochemical modelling and/or planetology, mantle geochemistry, noble gas geochemistry and surface/environmental geochemistry. They should have shown an ability to conduct an innovative research program.

We offer: The Isotope Geochemistry facility at ETH is one of the best equipped mass spectrometry laboratories worldwide, including high resolution multicollector ICP-MS, TIMS, laser ablation coupled with ICP-MS and an extensive noble gas mass spectrometry laboratory. The facility has its own dedicated mechanical and electronics support. The Positions are initially opened for one year renewable up to six years, depending upon performance. The position can be filled starting January 2006. ETH Zürich specifically encourages female candidates to apply with a view toward increasing the proportion of female researchers. For further information see http://www.erdw.ethz.ch/institut.cfm?ID_Inst=2705 or contact Prof. Bernard Bourdon at Bourdon@erdw.ethz.ch

Your application: Applicants should submit a cover letter, a curriculum vitae, a list of publications, a statement of research interests and three letters of reference to Bourdon@erdw.ethz.ch Deadline for applications is November 15, 2005 or until suitable candidates are found.

FACULTY POSITIONS
LONG ISLAND UNIVERSITY

The Division of Pharmaceutical Sciences seeks highly qualified individuals for tenure-track faculty positions in Medicinal Chemistry/Pharmacology and Pharmaceutics/Industrial Pharmacy. Appointment can be at any professional level, depending on experience and qualifications. All candidates must have a Ph.D. degree. Postdoctoral or equivalent experience is desired; a B.S. or Pharm.D. in Pharmacy is a plus. The successful candidate should have excellent communications and interpersonal skills and should demonstrate that they will be able to contribute effectively to the Division's teaching mission at both the professional and graduate levels.

Applications should include a cover letter, full CV, a selection of reprints, a list of three references and a statement of research and teaching goals. Send application to:

Dr. Fotios M. Plakogiannis
Director Division of
Pharmaceutical Sciences
Arnold & Marie Schwartz College of
Pharmacy and Health Sciences
Long Island University
75 DeKalb Avenue
Room HS 604
Brooklyn, NY 11201

Coriell Institute For Medical Research

Camden, NJ

President and Chief Executive Officer

Coriell Institute for Medical Research announces a search for a President and Chief Executive Officer. Coriell Institute is an internationally known not-for-profit, basic biomedical research institution established by Dr. Lewis L. Coriell, M.D., Ph.D. in 1953.

Coriell's research programs encompass the study of stem cells, primarily the biology of adult stem cells. Investigations of stem cells of the pancreas, fatty tissue, muscle, nervous system, and blood-forming system are currently underway at the Institute, as well as the banking of umbilical cord blood for therapeutic purposes. In addition, Coriell investigators pursue human genetic variation studies, including non-human primate research.

Most notably, Coriell Institute for Medical Research serves the entire scientific community by maintaining the world's largest collection of living human cells. Coriell has provided cell cultures and DNA to researchers all over the world, serving as the basis for groundbreaking discoveries in countless diseases, including Huntington's disease, Alzheimer's disease, cystic fibrosis and hypercholesterolemia. More than 135,000 cell lines and more than 315,000 vials of DNA have been distributed from Coriell's repositories to researchers in 61 nations, resulting in over 19,600 published citations.

The President and Chief Executive Officer will have responsibility for building strategic initiatives that drive the institute in the rapidly developing areas of human genetics and cell biology. He/She will be expected to encourage dialogue and increase awareness within and among the scientific and general communities about the genetic revolution and the possibilities and expectations of science. Candidates for this position should have a Ph.D. or M.D. degree with a sustained record in scientific research and administration and a national reputation that has resulted in national/international recognition.

The search is beginning immediately and for best consideration applications should be received as soon as possible. Requests for information, written nominations and application materials may be directed in confidence to:

Gregory Button, Senior Client Partner, or Arnie Sherrin, Senior Client Partner, Korn/Ferry International, 1835 Market Street, Suite 2000, Philadelphia, PA 19103; E-Mail (preferred): chris.redding@kornferry.com; 215-496-6666 (Telephone); 215-568-9911 (Fax).

For more information about the Coriell Institute for Medical Research please visit the website at **www.coriell.org**.

The Coriell Institute for Medical Research and Korn/Ferry are Equal Opportunity Employers that actively seek diversity in their workforce.

POSITIONS OPEN

TENURE-TRACK ASSISTANT/ASSOCIATE PROFESSOR

At Case Western Reserve University, the Center for Global Health and Diseases seeks faculty at the Assistant or Associate Professor level. The successful candidate with a graduate and/or medical degree will have interests in parasite genetics, epidemiology, population biology, or immunology, although other interest areas may be considered. Faculty responsibilities will be predominantly research (tenure track), and appointment will be in the Division of General Medical Sciences, with opportunity for joint appointments in other Case departments. A generous startup package and access to graduate students and a wide array of core facilities are available. The Center functions as an independent department at Case, and external grant support provides approximately $5.8 million annually. Currently nine faculty and 74 staff/students are based in a new facility offering 14,000 square feet of well-appointed laboratory space. Please send curriculum vitae, summary of professional and research goals, and names/addresses of three references to:

Dr. James W. Kazura
Professor and Director
Center for Global Health and Diseases
Case Western Reserve University
Wolstein Research Building
Room 4129, 2103 Cornell Road
Cleveland, OH 44106-7286

Case is an Equal Opportunity/Affirmative Action Employer.

The interdepartmental Computational Biology Program of the University of Colorado School of Medicine is soliciting applications for computational biology and bioinformatics **FACULTY** at the junior and senior levels. The recruitment spans all departments, and is open to scientists doing outstanding computational research relevant to any aspect of human health. Topics of interest include (but are not limited to): whole genome comparison, polymorphism analysis, informatics related to type 1 diabetes or autoimmune diseases, cancer informatics, neuroinformatics, and mass spectrometry informatics. Recruitment packages include substantial startup resources and extensive space at the new Fitzsimons campus. To apply, please send your curriculum vitae, names of at least three references, and a statement of teaching and research interests to: **Bioinformatics Search Committee, c/o Kathy Thomas, University of Colorado Health Sciences Center at Fitzsimons, Mailstop 8303, P.O. Box 6511, Aurora, CO 80045-0511.** Or send to **e-mail: kathy.r.thomas@uchsc.edu.** Review of applications will begin immediately and continue until the position is filled. The University of Colorado offers a full benefits package. Information on University benefits programs, including eligibility, is located at **website: http://www.uchsc.edu/pbs/.** *The University of Colorado is committed to Diversity and Equality in Education and Employment.*

FACULTY POSITIONS
Tenure Track
Department of Psychiatry

The Department of Psychiatry and the Center for the Study of Traumatic Stress at the Uniformed Services University of the Health Sciences (USUHS) seeks to fill tenure-track neuroscience laboratory research and teaching positions (**ASSISTANT/ASSOCIATE PROFESSOR**). The Department, 20 full-time faculty, seeks to expand ongoing neuroscience research, animal and human, in: stress, anxiety (particularly acute stress responses, PTSD, and dissociation), depression, behavior, and drug use. Individuals who hold Ph.D. or M.D. degrees and have active, fundable research are invited to apply. Send curriculum vitae, description of current and anticipated research, and three references to: **Robert Ursano, M.D., Chairman, Department of Psychiatry, USUHS, 4301 Jones Bridge Road, Bethesda, MD 20814-4799. E-mail rursano@usuhs.mil.** Applications should be received before December 1, 2005. *The University is an Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

ASSISTANT PROFESSOR IN PLANT BIOLOGY TENURE TRACK

The Department of Biological Sciences at Union College invites applications for a tenure-track Assistant Professor position in plant biology to begin in September 2006. The successful candidate will team-teach an interdisciplinary, introductory course in environmental studies, develop a course in biostatistics and in an area of expertise, and participate in the introductory biology sequence. Applications are encouraged from candidates with strong quantitative skills whose research focuses on organismal or ecological aspects of plant biology; area of specialty might include physiological ecology, population genetics, plant-animal interactions, aquatic ecology, ecosystems or landscape ecology. A Ph.D. and strong commitment to undergraduate education is required, postdoctoral experience is preferred.

Union College is a highly selective liberal arts college with a strong tradition of research and teaching in the sciences and engineering (**website: http://www.union.edu**). Please send a letter of application with curriculum vitae, statements of research interests and teaching philosophy, up to three authored publications, and three letters of reference to: **Dr. Steven Rice, Plant Biology Search, Department of Biological Sciences, Union College, Schenectady, NY 12308.** Review of applications will begin on November 11, 2005. *Union College is an Equal Opportunity Employer and strongly committed to increasing the diversity of its work force.*

YALE UNIVERSITY SCHOOL OF MEDICINE
Department of Genetics

The Department of Genetics at the Yale University School of Medicine is seeking outstanding candidates to fill tenure-track positions at faculty ranks commensurate with experience. The successful applicants will be provided generous startup funds and space and will establish strong independent research programs; we are broadly interested in genetics and genomics, with particular interest in vertebrate model organisms, cancer, and human genetics/genomics. Curriculum vitae, a brief statement of research plans, and three letters of recommendation should be sent to:

Richard P. Lifton, M.D., Ph.D.
Chairman, Department of Genetics
Yale University
School of Medicine
P.O. Box 208005
New Haven, CT 06520-8005

An Equal Opportunity/Affirmative Action Employer. We strongly encourage applications from women and minority candidates.

FACULTY POSITION IN PLANT GENETICS
Rutgers University

Applications are invited for a tenure-track position from individuals using genetic approaches to conduct cutting-edge research in plant biology. We are especially interested in applicants whose research involves the dissection of developmental or signal transduction pathways, the study of chromatin organization, or the analysis of genomes. The appointment can be made at any level from **ASSISTANT** to **FULL PROFESSOR**. The successful applicant will be expected to develop and maintain a successful, externally funded research program and to teach at the undergraduate and graduate level. Applicants should send curriculum vitae, with a list of publications and a brief description of research plans, and have three confidential letters of reference sent to: **Chair, Plant Biology Search Committee, Waksman Institute, Rutgers University, 190 Frelinghuysen Road, Piscataway, NJ 08854-8020.** The committee will begin its review of applications on November 1, 2005. Applications will be accepted until the position is filled. Starting date is September 1, 2006. *Rutgers University is an Equal Opportunity Employer.*

POSITIONS OPEN

ASSISTANT PROFESSOR IN ANIMAL PHYSIOLOGY OR BIOMECHANICS TENURE TRACK

The Department of Biological Sciences at Union College invites applications for a tenure-track Assistant Professor position in animal physiology or biomechanics to begin in August 2006. The successful candidate will develop courses in vertebrate anatomy and in his or her specialty, and participate in the biology introductory sequence. We seek a Biologist interested in collaborating with members of our engineering faculty and participating in an interdisciplinary program in bioengineering. This position includes funding for a reduced first-year teaching load, summer salary, and research startup funds from a Howard Hughes Medical Institute grant. We are particularly interested in applicants with research expertise in one or more of the following areas: systems physiology, biomechanics, or neurobiology. A Ph.D. and a strong commitment to undergraduate education required. Postdoctoral experience preferred. For information see **websites: http://www.union.edu** and **http://bioengineering.union.edu.**

Please send a letter of application with curriculum vitae, statements of research interests and teaching philosophy, up to three authored publications, and three letters of reference to: **Dr. Robert Olberg, Department of Biological Sciences, Union College, Schenectady, NY 12308.** Review of applications will begin on November 11, 2005. *Union College is an Equal Opportunity Employer and strongly committed to increasing the diversity of its work force.*

REGIS UNIVERSITY
Denver Colorado

The Psychology Department's Neuroscience program is seeking applications for a tenure-track **ASSISTANT** or **ASSOCIATE PROFESSOR** position in behavioral neuroscience. We are looking for a Ph.D. who will be expected to develop and maintain an excellent empirical research program, and engage bright, motivated undergraduates in his/her research. Preferred research areas relate to the investigation of animal models. The successful candidate must be able to teach neuroanatomy and neurophysiology, learning with animal laboratories, psychopharmacology, and his/her own area of interest.

Please send curriculum vitae, statements of research and teaching interests, three letters of recommendation, and evidence of teaching effectiveness and research activities to: **Dr. Jose Lafosse, c/o Dean of the College, 3333 Regis Boulevard E-24, Denver, CO 80221.** All materials should be submitted by November 11, 2005.

In accordance with its Jesuit Catholic mission, Regis University is committed to maintaining an inclusive living, learning, and working environment in which the gifts and civil rights of every individual are recognized and respected. Regis University does not unlawfully discriminate in either the provision of educational services or in employment practices on the basis of any human differences or other characteristics protected by local, state, or federal law and encourages applications from historically underrepresented groups.

Mercer University - Macon, GA. The Department of Environmental Science in the College of Liberal Arts announces its search to fill a tenure-track position at the rank of **ASSISTANT PROFESSOR.** The primary instructional responsibilities will be meteorology, introductory environmental science, and an upper-division course in the candidate's specialty. Additional responsibilities will include mentoring of undergraduate student research, and support of the College's interdisciplinary curriculum. Faculty duties commence August 1, 2006. Mercer University is a comprehensive institution of 7,000 students enrolled in 10 colleges and schools. The University and College associate a rich, Baptist heritage with educational programs distinguished by their rigor and academic freedom. Candidates who will complete all Ph.D. requirements from an accredited university/college by the commencement of faculty duties should apply online at **website: http://www.mercerjobs.com.** Review of applications will begin immediately. *Affirmative Action/Equal Opportunity Employer/ADA.*

Basic Scientist in the Biology of Aging Division of Gerontology Beth Israel Deaconess Medical Center Boston, Massachusetts

Beth Israel Deaconess Medical Center and Harvard Medical School are seeking an independent Ph.D. or M.D. basic scientist to develop and lead a new program in the biology of aging. The successful candidate will be experienced in the genetics and molecular biology of aging. Candidates must qualify for an appointment as Associate Professor of Medicine at Harvard Medical School, have a track record of consistent NIH funding and maintain an interest in the translation of basic research findings into the prevention of human disease and disability. A variety of model systems and laboratory techniques will be considered.

Please send applications or nominations, together with a cover letter, a current curriculum vitae and three letters of recommendation, to:

Lewis A. Lipsitz, MD
Chief of Gerontology
Beth Israel Deaconess Medical Center
110 Francis Street, Suite 1A
Boston, Massachusetts 02215

Beth Israel Deaconess Medical Center and Harvard Medical School are Equal Opportunity Employers. Women and minorities are particularly encouraged to apply.

BIOINFORMATICS / COMPUTATIONAL BIOLOGY

Wadsworth Center invites applications for tenure-track positions in Bioinformatics and Computational Biology. Successful candidates will expand Bioinformatics research and core activities. The Wadsworth Bioinformatics Center is housed in a new NIH-supported facility, with state-of-the-art computer clusters and collaboratory resources, and is closely integrated with experimental biologists working in a variety of disciplines, including genetics, structural biology, and infectious disease.

Laboratory Chief: Ph.D. or M.D., renowned senior scientist with administrative experience to lead the Bioinformatics group.

Bioinformatics Scientists: Ph.D. or M.D., focused on development and application of statistical or computational approaches to fundamental biological problems in genomics, RNAomics or proteomics.

Computational Biologist: Ph.D., in the field of Structural Biology, with experience in simulations. This individual will be part of a new Center for Molecular Machines, and will interact with scientists using cryo-EM, NMR and X-ray crystallography.

Core Director: Ph.D. or M.D., with excellent communication and management skills, interest in interacting with a multidisciplinary community of scientists, and an innovative record in computational biology. The Core collaborates with Wadsworth scientists in the design, analysis and interpretation of experiments, and assists in preparation of grant proposals.

Biostatisticians: Ph.D. or equivalent experience, skilled in development and application of statistical methods to genomics and proteomics data.

Bioinformatics specialists: B.S. or M.S., with expertise in data management, statistical analysis or programming.

Wadsworth Center enjoys a century of excellence as a research-intensive institution and is the country's most comprehensive state public health laboratory. With 200 doctoral-level scientists, Wadsworth provides a dynamic environment focused on the molecular, cellular and genetic aspects of disease. Wadsworth houses national centers in biological imaging and nanobiotechnology, and provides outstanding core facilities. Its location in Albany offers a wide range of cultural and recreational attractions and proximity to New York City, Boston and Montreal.

A CV, statement of research and/or service interests, and three letters of recommendation should be sent to bioinformatics@wadsworth.org by November 1, 2005. Applications received after that date will be considered on an as-needed basis. AA/EOE

Wadsworth Center
New York State Department of Health
Science in the Pursuit of Health®

www.wadsworth.org

2004 Best Places to Work in Academia . 2005 Best Places to Work for Postdocs

VERTEX

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Vertex Pharmaceuticals Incorporated is leading the way in small molecule drug discovery. By pioneering new, innovative, faster approaches to drug discovery with a focus on chemogenomics, our goal is to set the standard for pharmaceutical research and development in the 21st century. We currently have the following opportunities in our **Cambridge, MA** location.

DIRECTOR, PHARMACOLOGY, 4100-01B

RESEARCH SCIENTIST I/II, IN VIVO PHARMACOLOGY I/II, 4130-01B

We provide a highly stimulating working environment coupled with a high level of professional and intellectual challenge. In addition to competitive salary and benefits, we also offer equity participation and participation in a stock purchase program. No agencies, please. Apply online at: **www.vrtx.com**. EOE

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We Enjoy a Big Lead in Small Molecules.

National Institute on Aging

NATIONAL INSTITUTES OF HEALTH

Department of Health and Human Services National Institutes of Health National Institute on Aging Behavioral and Social Research Program (BSR)

http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch
Noncitizens with valid work visas and permanent residents may apply
Recruiting Health Scientist Administrators!!

BSR is seeking staff with expertise in behavioral/population genetics, or strong genetics/social science research, to provide scientific leadership and define short-range and long-term goals for research integrating genetics and the social-behavioral sciences in studies of aging.

We are also seeking staff with expertise in population and biological sciences to plan and develop an interdisciplinary portfolio of research and training grants, drawing on the intersection of population sciences, genetics, and evolutionary theories of aging. Experience with biomarkers, clinical physiology, physical anthropology, and performance measures in large-scale longitudinal studies and surveys is a plus.

The successful candidates will demonstrate independent research experience plus progressive responsibility in research program administration. These positions will challenge individuals with vision, skills and insight to take growing programs to new heights.

Salary is commensurate with qualifications and research experience, and time for independent research may be negotiated. For qualifications, evaluation criteria, and application instructions see **http: www.usajobs.opm.gov/**. Search by **Vacancy Announcements NIA-05-66442A and B**. For info contact **Pat Boyce** at **410-558-8032**. Applications must be received by **November 15, 2005**.

DHHS and NIH are Equal Opportunity Employers.

POSITIONS OPEN

WASHINGTON STATE UNIVERSITY

PHYSIOLOGIST

The Department of Veterinary and Comparative Anatomy, Pharmacology, and Physiology (VCAPP), College of Veterinary Medicine, Washington State University invites applications for a tenure-track position in integrative physiology at the rank of **ASSISTANT** or **ASSOCIATE PROFESSOR** to begin July 1, 2006, or earlier. Applicants must have a Ph.D. degree in physiology, neuroscience, bioengineering, cell biology, or a related discipline, and at least two years of postdoctoral research experience.

The successful applicant will be expected to develop and maintain an extramurally funded research program that compliments Department strengths, which include sleep physiology and function, neural and endocrine control of food intake and body weight, and cardiovascular and muscle physiology and biophysics.

Duties include teaching systems-level physiology to students of veterinary medicine and integration of physiological systems concepts into the curriculum. Additionally, the successful applicant is expected to teach integrative physiology in graduate programs.

Screening of applications will begin November 28, 2005. The application must include a cover letter, rank sought, curriculum vitae, description of teaching experience, statement of teaching philosophy, summary of research interests and goals, and names and contact information (including e-mail addresses) for three references. Send application materials to: **Physiologist Search Committee, Department of VCAPP, Washington State University, Pullman, WA 99164-6520** or **e-mail: bmorton@vetmed.wsu.edu.** *Equal Employment Opportunity/Affirmative Action/ADA.*

FACULTY POSITIONS
Microbiology and Immunology

The Department of Microbiology and Immunology invites applications for faculty positions at the **PROFESSOR, ASSOCIATE PROFESSOR AND ASSISTANT PROFESSOR** level. We are interested in investigators with strong research programs in molecular microbiology or molecular pathogenesis, including bacteriology, parasitology, mycology and virology; and molecular immunology. Candidates at the Professor and Associate Professor levels must have significant research accomplishments, active competitive grants, and a strong and consistent record of peer reviewed funding. Candidates at the Assistant Professor level should have the ability to establish and maintain a vigorous research program supported by peer-reviewed funding. Candidates must demonstrate a commitment to excellence in educating graduate and professional students. Startup funds and newly renovated laboratory space is available for the appointed investigators. The Department of Microbiology and Immunology is supported by extensive peer-reviewed funding (in excess of $400,000 per faculty position) and has a very strong graduate program supported by an NIH Training Grant.

Candidates should submit curriculum vitae, a statement of research accomplishments and future research plans, and should arrange for four letters of reference to be sent to: **Dr. Chris D. Platsoucas, Professor and Chairman, Department of Microbiology and Immunology, Temple University School of Medicine, 3400 North Broad Street, Philadelphia, PA 19140.** *Temple University is an Equal Opportunity/Affirmative Action Employer and specifically invites and encourages applications from women and minorities.*

FACULTY POSITION in Macromolecular Structure and Mechanism, Department of Biochemistry, Brandeis University. The Department of Biochemistry at Brandeis University is a group of biochemists and biophysicists whose research is focused on understanding the fundamental mechanisms by which macromolecules or macromolecular assemblies underlie biological function. We are seeking candidates with demonstrated research accomplishments in this field for a tenure-track faculty position, preferably at the **ASSISTANT PROFESSOR** level, to begin fall 2006. In addition to being outstanding researchers, candidates for this position should possess commitment to and skills for graduate and undergraduate teaching. To apply send curriculum vitae, along with a summary of current and proposed research and three letters of reference to:

Professor Christopher Miller
Howard Hughes Medical Institute
Mailstop 013
Department of Biochemistry
Brandeis University
Waltham, MA 02454-9110

First consideration will be given to applications received by October 31, 2005. *Brandeis University is an Equal Opportunity Employer, committed to building a culturally diverse intellectual community, and strongly encourages applications from women and minority candidates.*

Applications are invited for a tenure-track position in freshwater ecology or fisheries science at the **ASSISTANT PROFESSOR** level. Position is for nine-month teaching, research, and academic service. Summer salary is dependent upon availability of research grants. Incumbent is expected to teach undergraduate and graduate courses. Ph.D. degree in fisheries science or closely related area is required. Preference is for individuals with demonstrated ability to obtain extramural funding and expertise in one or more of the following areas: fisheries management (including fish population dynamics or genetics), pond or reservoir fisheries, and stream ecology (including aquatic habitat assessment and manipulation). Applicants should submit letter of interest describing qualifications for the position, statement of educational philosophy and research interests, curriculum vitae, transcripts, and names and contact information for five references. All items should be sent to: **Reynaldo Patiño, Chair, Search Committee, Texas Cooperative Fish and Wildlife Research Unit, Agricultural Science Building, Room 218, 15th and Boston, Lubbock, TX 79409-2120. E-mail: reynaldo.patino@ttu.edu.** Review of applications will begin 15 November 2005 and continue until position is filled. *Texas Tech University is an Equal Employment Opportunity/Affirmative Action Institution.*

NEUROBIOLOGIST
ASSISTANT PROFESSOR

The Department of Biological Sciences, California State University, Los Angeles invites applications for a tenure-track Assistant Professor position in the field of neurobiology. Applicants must have either a Ph.D. or M.D. degree and minimum of one year relevant postdoctoral experience. The selected candidate will be expected to develop a productive, independently funded research program involving undergraduate and graduate students, and teach undergraduate courses (including cell biology) and graduate courses in his/her area of expertise. Applications from glial and stem cell researchers are particularly encouraged. Startup funds available. Please submit letter of application, curriculum vitae, statements of research plans and teaching philosophy, and three letters of reference to: **Dr. Amelia Russo-Neustadt, Department of Biological Sciences, California State University, Los Angeles, 5151 State University Drive, Los Angeles, CA 90032.** Inquiries may be sent to **e-mail: arusson@calstatela.edu.** Position open until filled. Review of completed applications will begin November 15, 2005. *Equal Opportunity/Title IX/ADA Employer. Qualified women and minorities are encouraged to apply.*

New Mexico Tech
SCIENCE · ENGINEERING · RESEARCH · UNIVERSITY

NANOSCIENCE TENURE-TRACK POSITION AT NEW MEXICO TECH

New Mexico Institute of Mining and Technology seeks applicants for a nanoscience Tenure-Track Position to begin August of 2006. Candidates with exceptional qualifications may be considered for appointment at a higher rank. A Ph.D. in science or engineering, with research expertise in nanoscience, is required. Postdoctoral experience is preferable. The successful applicant will join an academic department appropriate to his/her teaching and research expertise. A joint appointment between two departments is encouraged. This position is of an interdisciplinary nature with the long-term goal to build a statewide program in nanoscience, in collaboration with other researchers from the state and in the framework of an EPSCoR Infrastructure Improvement Grant (**website: http://www.nmepscor.org/index/php**). Strong ties to the home curricular department(s) will assist the successful applicant in establishing strong research and curricular programs. A commitment to quality teaching is essential. Applicants should send curriculum vitae, copies of transcripts, a statement of research interests and teaching philosophy to: **New Mexico Tech, Wells Hall, Box 123, Socorro, NM 87801.** For full consideration, all materials must be received by November 28, 2005; however, the position will remain open until filled. For additional information about New Mexico Tech, visit our **website: http://www.nmt.edu/hr.** E-mail applications are not accepted. *Affirmative Action/Equal Opportunity Employer.*

ASSOCIATE DIRECTOR
Northern Great Plains Center for People and the Environment

The University of North Dakota's (UND) Northern Great Plains Center for People and the Environment (NGP CP&E) seeks an Associate Director to provide joint administrative leadership to a growing multi-disciplinary organization.

Associate Director will work closely with Director to: diversify funding; assist operation of a multi-disciplinary, multi-institution, multi-sector research and education organization; prepare proposals and reports; develop strategic plan; oversee execution of policies and programs; organize meetings and conferences; participate in Earth System Science and Policy degree program.

Ph.D. or equivalent in a discipline related to global environmental issues, scientific, socioeconomic, or policy oriented; stature within field, qualifying applicant for professorial rank; history of successful external funding; commitment to sustainability; team-building leadership; vision and innovativeness; excellent communications skills within and without academia; political astuteness. Twelve-month, nontenure-track position; open until filled.

The NGP CP&E is a Center of Excellence at the University of North Dakota committed to sustainability. It offers graduate degrees in earth system science and policy. Research is geared toward societal benefits. Significant growth underway in startup of National Suborbital Education and Research Center, operating NASA's DC-8 airborne laboratory. Personnel collaborate with investigators from seven other universities in the Upper Midwest Aerospace Consortium. See **website: http://www.umac.org.**

Send detailed letter of application describing fit to position, curriculum vitae, and list of five references to: **Dr. George Seielstad, Northern Great Plains Center for People and the Environment, University of North Dakota, Grand Forks, ND 58202-9011. Telephone: 701-777-4755; fax: 701-777-2940; e-mail: gseielst@aero.und.edu.** *UND is an Equal Opportunity/Affirmative Action Employer.*

OncoMed
PHARMACEUTICALS

OncoMed Pharmaceuticals Inc. is engaged in groundbreaking research that enables the development of innovative medicines targeting cancer stem cells. We are seeking outstanding individuals for the following positions with a strong desire to work in a dynamic start-up environment.

Scientist, Antibody Development: This Scientist will have experience in phage display and other antibody technologies. The qualified candidate will be a highly motivated and productive researcher able to develop novel strategies for antibody optimization. Qualified candidates must have a Ph.D. and postdoctoral experience in molecular biology and protein biochemistry. Industry experience is a plus.

Sr. Scientist, Cancer Biology: This Scientist will lead a group establishing new models for *in vivo* tumor growth and metastasis and developing novel therapies targeting cancer stem cells. Qualified candidates must have a Ph.D. and postdoctoral experience. Industry experience in drug discovery for anti-cancer therapeutics is highly preferred.

Scientist, Molecular Cell Biology: The qualified candidate will be a versatile and creative Scientist engaged in investigating signaling mechanisms employed by cancer stem cells in tumor progression and metastasis. This Scientist will be responsible for developing cell-based assays and pharmacodynamic markers useful for evaluating novel drug candidates. The position requires a Ph.D. and postdoctoral experience.

Send CV to:

Human Resources
OncoMed Pharmaceuticals, Inc.
265 N Whisman Road
Mountain View, Ca 94043

hr@oncomed.com
Phone: 650-938-9400
Fax: 650-938-4570

THE CLEVELAND CLINIC FOUNDATION
LERNER RESEARCH INSTITUTE

FACULTY POSITIONS
IN DEPARTMENT OF CELL BIOLOGY
Diabetes, Obesity, Metabolic Syndrome

The Department (**www.lerner.ccf.org/cellbio/**) is undergoing substantial expansion and will be hiring several new faculty at all ranks. Particular focus for this round of recruitment will be research broadly related to the cell biology of diabetes, obesity, or metabolic syndrome, including islet cell transplantation. Applicants with M.D., Ph.D. or dual degrees will be considered, with co-appointment to appropriate clinical departments available. Applicants must have strong potential to develop an active, independent research program. Outstanding facilities, generous start-up funds, and ongoing operational support are available. The Department's 19 primary faculty members lead strong programs in signaling, cell adhesion and growth regulation, apoptosis, intracellular trafficking, vascular biology, oxidative stress, regulation of gene expression, and regulation of mRNA translation and splicing. There is a strong tradition of collaborative research and well-developed training programs for both postdoctoral fellows and Ph.D. students. Interactions with outstanding clinical programs, including diabetes, bariatric surgery, cardiovascular medicine, and regenerative medicine are readily available, and all faculty are members of the Cell Biology Graduate Training Program at Case Western Reserve University School of Medicine.

Candidates should submit complete curriculum vitae, list of publications, brief statement of research interests, and three letters of reference to: **Roy L. Silverstein, M.D., Chairman, Department of Cell Biology, Lerner Research Institute, The Cleveland Clinic Foundation [NC10], 9500 Euclid Ave, Cleveland, OH 44195.** For specific questions contact **Ms. Teri Schantz 216-444-5221**, **schantt@ccf.org**.

The Cleveland Clinic Foundation is an Equal Opportunity/ Affirmative Action Employer.

FELLOWSHIPS

BECKMAN INSTITUTE
FELLOWS PROGRAM

Applications are invited for postdoctoral fellow appointments at the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign. The Beckman Institute is a multi- and interdisciplinary research center that focuses on three main research initiatives: Biological Intelligence, Human-Computer Intelligent Interaction, and Molecular and Electronic Nanostructures (www.beckman.uiuc.edu).

The Beckman Institute Fellows Program provides an excellent opportunity for young scholars to initiate a post-Ph.D. career of independent research in a stimulating and supportive interdisciplinary environment. The fields of research encompassed by the fellows program include the behavioral and biological sciences, chemistry, physics, and engineering.

Year 2006 Fellows will be appointed for up to three years, beginning as early as June 2006, and no later than December 31, 2006. Fellows receive $51,000/year, plus benefits and a research budget. Selection of Fellows is based on evidence of professional promise, capacity for independent work, outstanding achievement to date, and interdisciplinary research interests corresponding to one or more of the Institute's programs. To be eligible, Ph.D. must have been received no earlier than December 2002.

APPLICATION PROCEDURE:

Application forms available at www.beckman.uiuc.edu/fellows/postdoc/. Please direct questions to: cathyrix@uiuc.edu. DEADLINE: Applications must be submitted no later than Monday, December 5, 2005. Announcement of Fellows is made on or about March 8, 2006.

The Beckman Institute Fellows Program is supported by funding from the Arnold and Mabel Beckman Foundation. The University of Illinois is an Affirmative Action/Equal Opportunity Employer.

ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

LEAD SCIENTIST

CALFED BAY-DELTA PROGRAM

The California Bay-Delta Authority (CBDA), the implementing agency for the CALFED Bay-Delta Program (CALFED), seeks an established, experienced research scientist to direct the efforts of the Science Program as the CALFED Lead Scientist **(http://calwater.ca.gov)**.

This position requires: 1) Ph.D. or equivalent experience in natural science; 2) Evidence of stature in the broad scientific community; 3) Experience advising top managers and policy makers; 4) Evidence of the ability to work and communicate well with people from different professional backgrounds; 5) Experience working with and advising on complex issues that integrate multiple disciplines. Qualifications should be the equivalent of those for a federal GS-15 or higher.

For additional information about this recruitment, please see recruitment brochure: **www.cps.ca.gov/ExecutiveSearch/Recruitments/Brochures/LS_CBDA.pdf**.

The U.S. Geological Survey will be the host agency and the position will be for a multiyear term as an assignment to the USGS from any public, university or non-profit institution. Benefits will be covered through the home institution. The individual will be working out of the CBDA offices in Sacramento, CA. First review of application materials will begin November 14, 2005. The salary ranges from $104,000-$135,000.

To apply, send a letter of interest and curriculum vitae to **Stuart Satow** at:
CPS Executive Search
241 Lathrop Way, Sacramento, CA 95815
Ph. 916-263-1401
Fax: 916-561-7205
Email: resumes@cps.ca.gov

CPS
Executive Search
Formerly Shannon Executive Search

POSITIONS OPEN

Sandia National Laboratories

MASS SPECTROMETRY/ PROTEOMICS STAFF SCIENTIST

Sandia National Laboratories has an immediate opening for a Staff Scientist in mass spectrometry-based proteomics research at our Albuquerque, New Mexico, facility. The scientist will join Sandia's biosciences center in solving problems ranging from host-pathogen interactions, environmental remediation, and biodefense. The position requires technical knowledge in analytical chemistry, proteomics/protein sciences or a related biology field. Experience with MALDI-TOF and/or HPLC driven nanospray ionization TOF instrumentation and protein identification software is required. Experience in cell biology, microbiology, and protein separation and interaction assays is highly desired. The successful applicant will have experience writing proposals to federal funding agencies (such as DOE, DHS, NIH, and DOD) and working in multidisciplinary teams. Please submit resumes to: **Dr. Anthony Martino at e-mail: martino@sandia.gov (Subject: proteomics scientist).** *U.S. citizenship normally required. Sandia is an Equal Opportunity Employer.*

The Department of Biological Sciences at Idaho State University (**website: http://www.isu.edu/departments/bios**) invites applications for a tenure-track position in biochemistry at the **ASSISTANT/ASSOCIATE/PROFESSOR** level. Rank and salary will be determined by postdoctoral experience, publication record, and record of extramural funding. Teaching responsibilities may include undergraduate and graduate courses in biochemistry, as well as additional courses in the specialty area. Quality teaching, publication, extramural funding, and supervision of graduate students will be expected of the successful applicant. The specific area of research should complement existing departmental strengths, which include microbial biochemistry and research on extremophiles. Developing local/regional collaborations (Idaho Biomedical Research Institute, Idaho Accelerator Center, Idaho National Laboratory, etc.) will be encouraged. Review of applications will begin November 15, 2005 and continue until the position is filled. Send cover letter, curriculum vitae, statements of teaching and research philosophy/experience/goals, and three letters of reference to: **Dr. Larry Farrell, Biochemistry Search Committee, Department of Biological Sciences, Idaho State University, Pocatello, ID 83209-8007.** *Women and members of minority groups are particularly encouraged to apply.*

RESEARCH ASSISTANT PROFESSOR

Research Assistant Professor (nontenure-track) position is available in the Department of Neuroscience, Cell Biology, and Physiology to join research team studying synaptic transmission and plasticity in spinal cord. Must have doctoral degree and postdoctoral experience in neurobiological field. Prefer experience in electrophysiological studies of spinal cord. Submit letter of application, resume, and three references to: **Timothy C. Cope, Ph.D., Department of Neuroscience, Cell Biology, and Physiology, 3640 Colonel Glenn Highway, Dayton, OH 45435-0011.** Review of applications begins October 1, 2005, or open until filled. *Wright State University is an Affirmative Action/Equal Opportunity Employer.*

University of California, San Francisco/ Northern California Institute for Research and Education. POSTDOCTORAL POSITION available in signal transduction, tumor cell biology, bone metastasis, stem cell biology, and astrocyte biology. The successful applicant will have a Ph.D. in molecular and/or cell biology. E-mail or send curriculum vitae and names of two references to: **Dr. Lilly Bourguignon, Ph.D., Department of Medicine, VAMC (111N), 4150 Clement Street, San Francisco, 94121. E-mail: careers@ncire.org.** Job number 05-222.

POSITIONS OPEN

FACULTY POSITION
Experimental/Theoretical Interface between Physics and Life Sciences
Northwestern University

The Department of Physics and Astronomy together with the Department of Biochemistry, Molecular Biology and Cell Biology and the Department of Neurobiology and Physiology invite applications for a joint position at the interface of physics and the life sciences. The three departments represent a vibrant research and training environment within the college of Arts and Sciences, located on the Evanston campus of Northwestern University. Areas of interest include but are not limited to theoretical and experimental physics related to pattern formation in development, metabolic networks, computational neuroscience, and the function of cellular molecular machines. Applicants should submit a cover letter, curriculum vitae, research summary and statement of future research goals, and statement of teaching experience and interests and should arrange for four letters of recommendation to be sent on their behalf. Materials should be submitted electronically as PDF or Word files to **e-mail: physics-astronomy@northwestern.edu** using Physics/Life Sciences Search as the subject. Applications received by December 1, 2005, will receive full consideration, but the review will commence immediately and remain active until the position is filled. For more information about the three departments, the applicant is directed to **websites: http://www.physics.northwestern.edu; http://www.biochem.northwestern.edu; and http://www.northwestern.edu/neurobiology.**

Northwestern University is an Affirmative Action/Equal Opportunity Employer. Women and minorities are especially encouraged to apply.

ASSISTANT PROFESSOR
Ecology, Evolution, and/or Behavior

Princeton University's Department of Ecology and Evolutionary Biology invites applications for a tenure-track Assistant Professorship. We are interested in broad thinkers who will integrate research on environmental and organismal biology across ecology and evolution, including behavior, physiology, conservation biology, and biogeochemistry. Applicants should have a well-developed conceptual basis to their research and a strong commitment to teaching. A vision statement describing how specific research interests act to advance biology, curriculum vitae, three reprints, and three letters of recommendation should be sent to: **Dr. Lars Hedin, Department of Ecology & Evolutionary Biology, Guyot Hall, Princeton University, Princeton, NJ 08544-1003.** Screening of applications will begin 1 November 2005. For information about applying to Princeton and how to self-identify, please link to **website: http://web.princeton.edu/sites/dof/ApplicantsInfo.htm.** *Princeton University is an Affirmative Action/Equal Opportunity Employer.*

Department of Cell and Developmental Biology
University of Michigan Medical School

The Department of Cell and Developmental Biology at the University of Michigan Medical School invites applications for tenure-track **ASSISTANT, ASSOCIATE,** and **PROFESSOR** positions. We are seeking outstanding scholars with Ph.D., M.D. or equivalent degrees and relevant postdoctoral experience, who show exceptional potential to develop an independent research program that will address fundamental issues in cell or developmental biology. Applicants should send curriculum vitae, copies of up to three reprints, and a one- to two-page summary of research plans and should arrange to have three letters of reference sent directly by October 31, 2005, to:

Search Committee
Department of Cell and Developmental Biology
University of Michigan Medical School
4643 Medical Sciences Building II
1335 Catherine Street
Ann Arbor, MI 48109-0616

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.

POSITIONS OPEN

Sandia National Laboratories

IMMUNOLOGY/MOLECULAR BIOLOGY STAFF SCIENTIST

Sandia National Laboratories has an immediate opening for a Staff Scientist specializing in molecular immunology at our Albuquerque, New Mexico, facility. The scientist will join Sandia's biosciences center in solving problems in host-pathogen interactions, macrophage activation, and Toll-like receptor signaling. The position requires technical knowledge and experience in immunology, molecular biology, or related fields. Experience in microbial systems is highly desired. The successful applicant will join a multidisciplinary team focused on carrying out integrated research into state-of-the-art microengineered platforms for high throughput single cell analysis, proteomics, and computational systems biology. Experience writing grant proposals to federal funding agencies (e.g., DOE, NIH, DHS, and DOD) is required. Please submit resumes to: **Dr. Anthony Martino at e-mail: martino@sandia.gov (Subject: molecular immunology position).** *U.S. citizenship is normally required. Sandia is an Equal Opportunity Employer.*

BIOLOGY (ZOOLOGY) FACULTY POSITION

Illinois College invites applications for a full-time tenure-track faculty appointment in biology at the **ASSISTANT PROFESSOR** level beginning August 2006. The successful candidate will possess a Ph.D. in zoology or a related field, will be committed to teaching in the liberal arts setting, and will be expected to conduct research with undergraduate students. Teaching responsibilities will include an introductory course for biology majors; general zoology (invertebrate and/or vertebrate); marine biology (team-taught with laboratory in Florida Keys); and advanced courses in the applicant's area of expertise. Located in a newly constructed science center, the Biology Department enjoys a cooperative atmosphere with the other science departments. A full-time laboratory manager assists faculty in biology and chemistry. Each faculty member is provided with a research laboratory adjoining his/her office. Teaching and research are assisted by PCR/electrophoresis equipment, fresh/saltwater aquaria, florescence microscopy, an environmental growth chamber, sterile hood, greenhouse, and museum containing preserved plants and animals (e.g., insect collection, herbarium). Faculty are encouraged to participate in trips abroad (e.g., Costa Rica), and to collaborate with organizations external to the College (e.g., SIU School of Medicine).

Review of applications will begin on 1 October 2005. Preference will be given to candidates that have supervised undergraduate research. Interested candidates should submit a cover letter, curriculum vitae, statement of teaching philosophy, research plan, sample reprints, and three letters of recommendation to: **Biology Faculty Search Committee, c/o Dean of Academic Affairs, Illinois College, 1101 West College Avenue, Jacksonville, Illinois 62650.** For additional information see **website: http://www.ic.edu.** *Illinois College is an equal opportunity employer. Women and minority candidates are encouraged to apply.*

POSTDOCTORAL POSITION to study mTOR and Ras-related GTPases in inherited diseases and cancer. Experience in cell and molecular biology desired. Include curriculum vitae and e-mails for three references. Contact: **Dr. A.F. Castro, University of California, San Francisco Cancer Center, 2340 Sutter Street, San Francisco, CA 94115. E-mail: castroa@surgery.ucsf.edu.**

Baystate Health in Springfield, Mass

The Pioneer Valley Life Sciences Institute (PVLSI) seeks to fill **TWO Faculty positions (rank open)** who use vertebrate and/or invertebrate models to study developmental or degenerative processes relevant to human nerve and/or muscle disease. We welcome a variety of experimental approaches including physiology, genetics and molecular biology. Expertise in cell death particularly welcomed. Successful candidates will have an M.D. and/or Ph.D., significant post-doctoral experience and a record of developing and maintaining an extramurally funded research program.

The PVLSI (**www.PVLSI.org**) is an independent non-profit organization that is jointly managed and operated by Baystate Health System (**www.Baystatehealth.com**) and the University of Massachusetts Amherst (**www.UMass.edu**). Researchers will have the opportunity to work closely with physicians and basic scientists in a newly built and well-equipped facility. Applicants should submit curriculum vitae, statement of research plans, and three letters of reference to: **Dr. Lawrence Schwartz, PVLSI, 3601 Main Street Springfield, MA 01199** or via e-mail to **Lawrence.Schwartz@bhs.org** (PDF format preferred).

The PVLSI is an Equal Opportunity/ Affirmative Action Employer.

Lead Scientist (Full Professor) Molecular Imaging

The Department of Radiology at the Brigham and Women's Hospital, a teaching affiliate of the Harvard Medical School, seeks a seasoned researcher to assume an immediate leadership role (rank of Full Professor) within the Department of Radiology's *Functional and Molecular Imaging Program*. The position would be suitable for an MD, MD/PhD, or PhD Scientist. A unique opportunity exists to leverage existing, well-established programs in MRI, Surgical Planning, Focused Ultrasound, and Image-guided Therapy into a multimodality, multidisciplinary program in Molecular Imaging that integrates genomics, drug development, oncology, cardiology, neurology, and clinical trials.

A Biomedical Imaging Research Core Facility, presently in its planning stages, will feature a cyclotron, a radiopharmaceutical research lab (GMP); a research PET/CT system; and three MR units. These resources, along with existing initiatives within the Department of Radiology, will provide an essential research and technology development infrastructure to grow a program in Molecular Imaging.

Viable candidates will present a substantial research portfolio; a strong record of peer-reviewed publications; evidence of excellence in teaching; a history of successful program administration in an academic environment; and personal qualities demonstrating entrepreneurship, vision, and risk-taking.

Interested candidates should send a letter and curriculum vitae to:

Ferenc A. Jolesz, MD
B. Leonard Holman Professor of Radiology
Vice Chairman for Research
Director, Division of MRI and Image Guided Therapy Program
Department of Radiology
Brigham and Women's Hospital
Harvard Medical School
75 Francis Street, Boston MA 02115
Tel: 617 732 5961
Fax: 617 582 6033
E-mail: jolesz@bwh.harvard.edu

Applicants must be U.S. citizens or permanent residents of the United States.
The Brigham and Women's Hospital is an Equal Opportunity, Affirmative Action Employer.
Minority applicants are encouraged to apply.

CASE
CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF MEDICINE

Tenure Eligible Position: Director of Bioinformatics for the Case Center for Proteomics and Assistant/ Associate Professor of Genetics

The Department of Genetics and the Case Center for Proteomics and Mass Spectrometry in the School of Medicine at Case Western Reserve University invite applications for a tenure-eligible position at the Assistant or Associate Professor level. The position includes a primary faculty appointment in the Department of Genetics and a secondary appointment in the Case Center for Proteomics, with an appointment as Director of Bioinformatics for the Proteomics Center. The successful candidate will carry out research at the forefront of bioinformatics and systems biology research, with a special emphasis on sequence or structural analysis. The candidate will be an active participant in the expansion of the genomics and proteomics programs of the medical school, including the development of a new campus devoted to interdisciplinary, quantitative and populations based biomedical research. Candidates should have a Ph.D. and/or M.D. and relevant post-doctoral or industrial experience. Competitive start-up packages will be available.

Interested candidates should apply by **December 1, 2005** by sending a cv, a plan of research, and the names of 3 references to: **genetics-search@case.edu** or to: **Dr. J. Nadeau, Department of Genetics, BRB731, CWRU, 10900 Euclid Ave, Cleveland, OH 44106**.

In employment as in education, Case Western Reserve University is committed to Equal Opportunity and World Class Diversity. Case is a recipient of a National Science Foundation ADVANCE Institutional Transformation Grant to increase the participation of women in Science and Engineering.

FACULTY POSITION IN ECOLOGICAL GENETICS

The Departments of Molecular Biology and Botany at the University of Wyoming are seeking to fill a joint tenure-track position at the assistant professor level. We seek an interactive colleague with broad interests using innovative genetic or genomic approaches to study ecological questions. We are especially interested in individuals committed to studying ecological genetics in the context of community dynamics and/or global change. However, all qualified candidates will be considered. This position is the first of five to be filled in a new, NSF funded interdisciplinary Program in Ecology (**http://uwadmnweb.uwyo.edu/botany/Ecology/**). Candidates must hold a Ph.D. in an appropriate field and have at least 2 years of postdoctoral experience. Evidence of accomplishments in both research and teaching will be essential. The successful candidate will be expected to establish an independently funded research program and participate in both the undergraduate and graduate teaching programs. The new faculty member would be expected to teach a genetics course for one semester and an additional course in his or her specialty area. The Departments are presently composed of 26 faculty members with diverse research interests supported by numerous grants. Salary and start-up packages will be competitive. The University enrolls 12,000 students including approximately 2500 graduate students. Laramie is located in southeastern Wyoming about 120 miles from Denver, Colorado. For additional information about the University and departments, see **http://www.uwyo.edu/ag/molecbio/mobio.html** and **http://www.uwyo.edu/Botany/**. Any questions can be directed to **uwmbio@uwyo.edu**.

Candidates should email a curriculum vitae, descriptions of research plans and teaching philosophy, and three letters of recommendation to **uwmbio@uwyo.edu**. PDF formatting is preferred for these documents. Screening of applications will begin on **November 1, 2005** and continue until a suitable candidate is identified.

The University of Wyoming is an AA/EEO Employer.

POSITIONS OPEN

ECOLOGIST AND CHAIR
Department of Environmental Studies
Emory University

The Department of Environmental Studies in Emory College of Emory University invites applications for the position of **DEPARTMENT CHAIR** and **PROFESSOR** in the research area of ecology. Emory is an internationally known research university and will soon begin a comprehensive fundraising campaign to strengthen its research and teaching programs. The Department anticipates significant expansion over the next few years. The successful candidate for this position must have a distinguished record of extramurally funded research and scholarly activity sufficient to merit appointment at the rank of tenured Full Professor in Emory College. Applicants must have a doctoral degree or its equivalent in ecology, biology, or other appropriate discipline. Applicants should have excellent communication, leadership and administrative skills and should have a strong commitment to undergraduate and graduate teaching. The successful candidate will oversee the continued growth of the Department via the hiring of new faculty, the development of the undergraduate curriculum and graduate training, and the fostering of interdisciplinary research across the basic, social, and health sciences.

Please submit a cover letter, curriculum vitae, statement of research interests, experience and future plans, teaching philosophy, and departmental leadership philosophy. Materials should be submitted to: **Chair – Search Committee, Department of Environmental Studies, 400 Dowman Drive, Suite E-510, Math/Science Center, Emory University, Atlanta, GA 30322.** The review of applications will begin in early November 2005 and will continue until a suitable candidate is identified. Please visit the departmental **website: http://www.emory.edu/COLLEGE/ENVS,** to learn more about Environmental Studies at Emory. *Emory University is an Equal Opportunity Affirmative Action Employer. Women and underrepresented minority candidates are encouraged to apply for this position.*

ASSISTANT/ASSOCIATE/ FULL PROFESSORS –Tenure-Track Clinical and Translational Research
Texas Tech University Health Sciences Center
School of Pharmacy

The Pharmacy Practice Department has openings for 12-month tenure-track faculty positions in clinical and translational research. Although only 10 years old, the School of Pharmacy is ranked among the top 43 colleges of pharmacy with respect to federal research funding. Positions are state funded and offer remarkable opportunities for creative scientists. Qualifications include a Ph.D., Pharm.D., or M.D. and postdoctoral training. History of external competitive funding is strongly preferred. Preference will be given to investigators in the broad areas of aging, pediatric and adult pharmacology, and infectious diseases. Mass spectrometry and drug development experience a plus. Aggressive startup packages will be provided. Additionally, the school's multicampus structure (Dallas/Ft. Worth, Amarillo, and Lubbock) provides the infrastructure for multisite research. Positions are available at all campuses. Interested investigators should send their curriculum vitae, statement of research interest, funding history, teaching interests within a Pharm.D. and Ph.D. (biomedical sciences) program, and contact information for at least three references. Review of applications will commence immediately and continue until positions are filled. Address all correspondence to: **Dr. C.A. Bond, Professor and Search Committee Chair, Department of Pharmacy Practice, Texas Tech University Health Sciences Center, School of Pharmacy, 1300 Coulter, Amarillo, TX 79106. E-mail: cab.bond@ttuhsc.edu; telephone: 806-356-4000 ext. 244; fax: 806-356-4018.** Interested applicants must complete the online application process; visit our **website: http://jobs.texastech.edu.**

Equal Employment Opportunity/Affirmative Action Employer. Women and minorities are strongly encouraged to apply.

POSITIONS OPEN

ANATOMIST/HISTOLOGIST
Southern Illinois University, Carbondale

The Department of Anatomy invites application for a tenure-track faculty position at the **ASSISTANT PROFESSOR** level. Qualified candidates must have a Ph.D., M.D., or equivalent degree and at least two years of postdoctoral experience with demonstrated ability to perform independent research. Special (but not exclusive) consideration will be given to those with vigorous research interests in neuroscience, cancer, or cell biology. Opportunities for collaboration exist within several basic science and clinical departments and a newly formed Center for Integrated Research on Cognitive and Neural Science. Teaching experience in gross anatomy or histology is required and experience with problem based learning curricula is preferred. This is a security-sensitive position. Before any offer of employment is made, the University will conduct a preemployment background investigation, which includes a criminal background check. Effective date of employment is July 1, 2006; search will continue until position is filled. Provide curriculum vitae, a letter specifying teaching interests and research plans, and three letters of reference by December 1, 2005, or until filled to:

Search Committee, Department of Anatomy
School of Medicine, MC 6523
Southern Illinois University, Carbondale
1135 Lincoln Drive
Carbondale, IL 62901

Women and minority applicants are encouraged to apply.

TENURE-TRACK POSITIONS ORAL INFECTIOUS DISEASES

The Department of Oral Biology and Center for Oral Infectious Diseases at New Jersey Dental School (NJDS) are inviting applications for two tenure-track positions at the **ASSISTANT PROFESSOR** level. Candidates should have a Ph.D. and postdoctoral experience. Our primary research interests include host pathogen interactions, mechanisms of pathogenesis, and the role of biofilms in oral disease. Preference will be given to applicants working in the area of microbial pathogenesis and/or immunogenetics. The successful candidates will be expected to develop an innovative research program supported by external funding and to participate in the Department's graduate and undergraduate training programs.

NJDS offers competitive salaries and excellent benefits. Please send curriculum vitae, statement of research interests, and contact information for three references to:

Dr. Daniel H. Fine
Chair, Oral Biology Department
New Jersey Dental School - UMDNJ
185 South Orange Avenue, MSB - C-636
Newark, NJ 07103
E-mail: finedh@umdnj.edu

University of Medicine and Dentistry of New Jersey is an equal opportunity, affirmative action employer and encourages applications from minorities, women, and persons with disabilities.

ECOLOGY

The Department of Ecology and Evolutionary Biology at the University of Colorado seeks to fill a position for an ecologist at the **ASSISTANT PROFESSOR** level. We are especially interested in candidates with research interests in the area of behavioral ecology, conservation biology, or population biology. The individual will be expected to pursue active research programs and to teach in the undergraduate and graduate programs. Applicants should submit current curriculum vitae, statements of research and teaching interests, and four letters of reference to: **Ecology Search Committee, University of Colorado, 334 UCB, Boulder, CO 80309.** Review of applications will begin on October 15, 2005. *The University of Colorado at Boulder is committed to diversity and equality in education and employment.*

POSITIONS OPEN

DIRECTOR CLINICAL RESEARCH CENTER

The New Jersey Dental School is seeking a Director for its recently established Clinical Research Center. Candidates should be active investigators with the ability to conduct translational research leading to novel approaches for the diagnosis, treatment, and prevention of oral infectious diseases. The Director will be responsible for the design and oversight of clinical trials, as well as training clinical investigators and mentoring junior faculty. Preference will be given to candidates with experience bringing discovery from the laboratory to clinical application. Applicants should have active grant support and/or experience in conducting research for industry, as well as a combined D.D.S./Ph.D., M.D./Ph.D. or equivalent training.

We offer competitive salaries and excellent benefits. Applicants should send curriculum vitae and contact information for three references to:

Dr. Daniel H. Fine
Chair, Oral Biology Department
New Jersey Dental School - UMDNJ
185 South Orange Avenue, MSB - C-636
Newark, NJ 07103
E-mail: finedh@umdnj.edu

University of Medicine and Dentistry of New Jersey is an Equal Opportunity, Affirmative Action Employer and encourages applications from minorities, women, and persons with disabilities.

DEVELOPMENTAL BIOLOGIST
Bucknell University

Applications are invited for an entry-level, tenure-track **ASSISTANT PROFESSOR** position beginning August 2006 in the Department of Biology at Bucknell University. Ph.D. required. Teaching responsibilities will include an advanced course in animal developmental biology, participation in an introductory level course for biology majors, a non-majors course to support the general education program, and supervision of undergraduate research. A cover letter, statements of teaching philosophy and research goals, curriculum vitae, and three letters of recommendation should be submitted to:

Mitchell Chernin, Ph.D.
Chair, Biology Department
Bucknell University
Lewisburg, PA 17837
E-mail: chernin@bucknell.edu
Telephone: 570-577-1124
Fax: 570-577-3537
Website: http://www.bucknell.edu/department/biology/

Review of applications will begin on November 7, 2005. The search will remain open until the position is filled. *Bucknell University encourages applications from women and members of minority groups. Equal Employment Opportunity/Affirmative Action.*

ASSISTANT PROFESSOR OF BIOLOGY

Centre College seeks applicants for a tenure-track position beginning fall 2006. Successful applicant will hold a Ph.D. in the life sciences and expertise in physiology. Teaching duties include an upper division course in general and comparative physiology, development of a course in area of specialty, and introductory biology. Participation in the college's freshman studies and nonmajors natural sciences programs is also anticipated. Collaborative research with undergraduates is expected and supported. Send statements of teaching philosophy, research interests, curriculum vitae, transcripts, and three letters of recommendation to:

Dean John Ward
Vice President for Academic Affairs
Centre College
600 West Walnut Street
Danville, KY 40422

Review of applicants will begin November 1, 2005, and continue until position is filled. *Women and minorities are encouraged to apply. Centre College is an Equal Opportunity Employer.*

Featured Employers

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If you would like to be a featured employer, call 202-326-6534.

ScienceCareers.org
We know science AAAS

U.S. Department of Agriculture
Animal and Plant Health Inspection Service
Plant Protection and Quarantine
Center for Plant Health Science and Technology

The National Plant Germplasm and Biotechnology Laboratory (NPGBL) located in Beltsville, MD is recruiting for four full-time Plant Pathologists with strong credentials in the area of molecular biology, molecular genetics, and/or molecular detection. NPGBL is a unit of the Center for Plant Health Science and Technology and is the national laboratory responsible for non-routine testing and confirmation of plant pathogens of high consequence and many complex diseases and pathogens, or regulatory situations that threaten US agriculture or natural resources.

The successful incumbent will be part of a team of experimental and analytical scientists that develops solutions to existing and anticipated complex plant pathological problems such as those posed by the introduction of exotic high consequence plant pathogens. The incumbent's research will address the development, adaptation, modification, and validation of molecular and biochemical detection and differentiation techniques with a critical goal being determination of the effectiveness of current or novel molecular or immunological assays to identify and differentiate newly introduced plant pathogens of high agricultural and economic consequence. Applicants should have a strong track record in the development of precise methods and techniques to identify and differentiate strains or closely related plant pathogens, other suborganismal targets, and possibly elements of genetically modified organisms. The incumbent should have a record of technology/methods development and transfer of developed methods and techniques for implementation by user groups that will facilitate the exclusion by APHIS of foreign pathogens that may enter the U.S. in plant materials and commodities. The incumbent must demonstrate their ability to work collaboratively with colleagues from state, federal, university, industry, and international counterparts as a team leader and team member. Strong credentials in the area of molecular biology, molecular genetics, and/or molecular detection are desired. Method validation expertise and post-doctoral experience desired. Applicants must be a US citizen and pass a government security clearance. Salary ranges from $62,886.00 to $97,213.00.

For more details and application direction see **http://jobsearch.usajobs.opm.gov/** and enter announcement number **677-2005-0489** or **2477-2005-0375** in the keyword search box. All applications must be received by **October 17, 2005**. Questions may be directed to **Laurene Levy** at **(301) 504-7100**.

The Federal Government is an Equal Opportunity Employer.

VASGENE

VasGene Therapeutics, Inc. is a biopharmaceutical company engaged in the discovery, development, and commercialization of novel therapeutics based on vascular and tumor cell biology. We are seeking **talented, self-motivated scientists** with excellent credentials including peer reviewed publications **in molecular biology, protein chemistry, cellular biology, phage display, monoclonal antibody technology, and bio-informatics**. Experience in pharmaceutical discovery research is preferred. Outstanding leadership, communication, and writing skills are required.

Vasgene is in the process of relocating to Agoura/Westlake, a suburb Los Angeles with close access to beaches and mountains. Vasgene is also seeking research assistants/associates with a BS or MS and 3-5 years experience in the related fields. Our competitive compensation package reflects our strong commitment to hiring exceptional scientists.

Applicants are invited to send their resume by e-mail to:
admin@vasgene.com

FACULTY POSITION
CELL SIGNALING
BOSTON COLLEGE

We invite applications for a tenure-track faculty position in the area of **CELL SIGNALING**, in the Boston College Biology Department. This search is open to candidates at the level of **ASSISTANT PROFESSOR**, although exceptional candidates at the level of **ASSOCIATE PROFESSOR** or **FULL PROFESSOR** will be considered as well. The university provides extremely competitive start-up funds and research space with the expectation that the successful candidate will establish, or bring to the university, a vigorous, externally funded research program.

We seek a colleague whose research will mesh with that of one or more current faculty members with interests in computational biology, molecular and cell biology, developmental biology, genetics and genomics, signal transduction, neuroscience, cell cycle biology, and/or infection and immunity. Preference will be given to colleagues whose programs could enhance growing collaborations that involve the Biology, Chemistry, Physics, Computer Science, and Psychology departments at Boston College. The successful candidate will be expected to develop or bring a substantial funded research program, train graduate students, and participate in the teaching mission of the department.

Boston College is a doctoral-extensive university that is continuing to make substantial investments in the growth of its research programs in the natural sciences. These investments include the hiring in Biology of seven tenure-track faculty members over the past five years, and the recent completion of a $90 million expansion and renovation of research space for our Biology and Physics departments. The university is committed to continuing growth in Biology faculty line strength.

Applicants should submit a curriculum vitae and a statement of present and future research plans, and arrange to have three letters of reference sent to: **Cell Signaling Search Committee, Boston College Biology Department, 140 Commonwealth Avenue, Higgins Hall, Chestnut Hill, MA 02467**. Confidential inquiries regarding the position can be directed to the department chairperson, **Dr. Marc Muskavitch**, via email (**muskavit@bc.edu**). This appointment will begin on or after July 1, 2006. Applications should be received by **December 1, 2005** to assure full consideration. Review of applications will continue until the position is filled.

Boston College is an Affirmative Action, Equal Opportunity Employer.
Women and minority group members are especially encouraged to apply.

POSITIONS OPEN

THE UNIVERSITY OF WESTERN ONTARIO DEPARTMENT OF BIOLOGY

The Department of Biology at The University of Western Ontario invites applications for the following positions effective July 1, 2006. Successful candidates will hold a Ph.D. or equivalent and have a proven research record, including publications of high quality. Postdoctoral experience or equivalent will be an asset. The successful applicants will be expected to develop an innovative program of independent, externally funded research and to teach at both the undergraduate and graduate levels. In particular, we are looking for individuals who are able to work well with others.

INVERTEBRATE ZOOLOGY

This probationary (tenure-track) position will be at the **ASSISTANT PROFESSOR** level. The successful candidate will have research and teaching interests in and experience with invertebrates with special emphasis on evolution, comparative biomechanics, and functional morphology. Experience with marine invertebrates will be an asset. This enthusiastic individual would also contribute to the undergraduate Honours Program in related fields.

GENETICS

This probationary (tenure-track) position will be at the **ASSISTANT PROFESSOR** level. The successful candidate will have research interests that encompass the areas of molecular biology, genetics, evolutionary genetics, and/or genomics. The applicant should have a broad background and training in modern genetic and molecular techniques in order to contribute to the broad range of undergraduate courses offered by this Department. The successful candidate will be a member of the Molecular Genetics Unit within the Department of Biology and have access to a joint core facility and a dynamic research community in London. In particular, we are looking for an enthusiastic individual who is well versed in genetic and molecular principles and can contribute to the undergraduate Honours Program in Genetics and related fields.

Applications, including curriculum vitae, names and addresses of three references whom we may contact, copies of recent significant papers, and a one-page summary of proposed research should be forwarded to:

Dr. Brock Fenton, Chair
Department of Biology
The University of Western Ontario
London, Ontario N6A 5B7 Canada

We will not accept electronic applications. The deadline for applications is December 15, 2005.

Positions are subject to budget approval. Applicants should have fluent written and oral communication skills in English. *All qualified candidates are encouraged to apply; however, Canadian citizens and permanent residents will be given priority. The University of Western Ontario is committed to employment equity and welcomes applications from all qualified women and men, including visible minorities, aboriginal people, and persons with disabilities.*

POSTDOCTORAL POSITIONS
Washington University School of Medicine
NIH Training Program in Diabetes Research

Postdoctoral positions available in multi-investigator program to study diabetes and related endocrine diseases. Research opportunities in insulin secretion and action, insulin resistance in aging and HIV/AIDS glucose transporters, islet growth and proliferation, cellular differentiation, antigen presentation, T cell development, transport, storage and metabolism of lipids, obesity, mechanisms of vascular, neurological and pregnancy complications, diabetic eye disease, carbohydrate structure and function, channel electrophysiology. U.S. citizenship or permanent resident status is required. Send curriculum vitae to: **Dr. Michael L. McDaniel, Box 8118, Washington University School of Medicine, Department of Pathology and Immunology, St. Louis, MO 63110. Telephone: 314-362-7435; fax: 314-362-4096; e-mail: mmcdaniel@wustl.edu.**

RESEARCH ASSISTANT PROFESSOR. Nontenure-track position at the University of Illinois at Chicago, Department of Anesthesiology, for research in molecular biology and/or mitochondrial metabolism. Ability to work independently and establish needed procedures. Able to draft own publications from research studies. Salary commensurate with experience. For fullest consideration, submit applications by October 7, 2005, to: **Dr. June Palmer, University of Illinois at Chicago, Department of Anesthesiology, m/c 515, 1740 W. Taylor, Chicago, IL 60612.** *Affirmative Action/Equal Opportunity Employer.*

TWO TENURE-TRACK POSITIONS
ANIMAL PHYSIOLOGIST/BEHAVIORAL BIOLOGIST
ANIMAL PHYSIOLOGIST

The Department of Biology at William Paterson University (WPUNJ) invites applications for two tenure-track faculty positions at the **ASSISTANT PROFESSOR** level. Ph.D. required. Postdoctoral research and teaching experience preferred. Candidates are expected to develop a research program involving students. Teaching responsibilities for both positions will include some combination of graduate courses, undergraduate major courses, and anatomy and physiology courses for nonmajors.

Animal Physiologist/Behavioral Biologist with specialization complementing departmental concentrations in behavioral biology or ecology. Animal Physiologist with specialization complementing departmental programs in biotechnology or physiology/behavior.

The facilities of the Department include an established mouse laboratory, electron microscopy suites, well-equipped biotechnology laboratories, and a nearby pond with aquatic research facilities. The Department offers B.S. and M.S. degrees in both biology and biotechnology. Applicants should submit curriculum vitae, statement of research interests and teaching philosophy, names, addresses and telephone numbers of three references to: **Dr. Eileen Gardner, Chairperson, Department of Biology, Science Hall, William Paterson University, 300 Pompton Road, Wayne, NJ 07470.** Please indicate for which position you are applying. Review begins immediately and continues until the position is filled. *WPUNJ is an Affirmative Action/Equal Opportunity Institution, women and minorities are encouraged to apply.*

RESEARCH ASSOCIATE
Cellular/Molecular MRI

A Research Associate position is available for a Cellular/Molecular Biologist in the Department of Biological Sciences at Carnegie Mellon University. We have initiated a new program to develop novel agents for in vivo cellular/molecular imaging utilizing high-resolution magnetic resonance imaging (MRI). Previous experience with MRI is nonessential. This research is being conducted in conjunction with the Pittsburgh NMR Center for Biomedical Research, which is a state-of-the-art facility for small animal MRI. Candidates are required to have a Ph.D. with training and extensive experience in molecular and cell biology. Candidates should have a background in a broad range of recombinant DNA techniques, vector technologies, construction of viral vectors, gene expression detection methods (e.g., real-time PCR), and cell culture and have strong scientific problem-solving skills, ability to communicate results in a clear and concise manner verbally and in writing, and a record of scientific achievement as documented by peer-reviewed journal publications.

Interested candidates should send curriculum vitae and names of three references to: **Dr. Eric T. Ahrens, Department of Biological Sciences, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213 U.S.A. Fax: 412-268-7083; e-mail: eta@andrew.cmu.edu.** *Carnegie Mellon is an Equal Opportunity/Affirmative Action Employer.*

ASSISTANT PROFESSOR OF BIOLOGY
Microbiology and Immunology

The Biology Department at the University of Indianapolis seeks an exemplary teacher/researcher, beginning fall 2006, to fill a tenure-track position at the Assistant Professor level in the areas of immunology and microbiology. Candidates are expected to teach a variety of courses, and maintain an active program of mentoring undergraduate research.

Candidates must have an earned Doctorate (postdoctoral experience preferred) in the biological sciences or related area. They should demonstrate strong potential for outstanding teaching, and possess excellent verbal and written communication skills.

Salary is competitive and commensurate with experience and qualifications. Interested candidates should submit a letter of application, curriculum vitae, unofficial transcripts, statement of teaching philosophy, statement of research interests, and three references including contact information to:

Biology Search Committee
Department of Biology
University of Indianapolis
1400 E. Hanna
Indianapolis, IN 46227

Review of applications will begin on November 4, 2005, and continue until the position is filled. Inquiries should be directed to: **Department Chair, Mark Harrison, e-mail: harrison@uindy.edu.** *The University of Indianapolis is an Equal Employment Opportunity /Affirmative Action Employer and encourages applications from women and minorities.*

BIOCHEMIST

East Tennessee State University Biological Sciences invites applications for a tenure-track **ASSISTANT PROFESSOR** in biochemistry, beginning August 15, 2006. Ph.D. required by start date, postdoctoral experience preferred. Research in any area of biochemistry including macromolecule structure/function, metabolism, and use of systems approaches will be considered. Research activities must include B.S. and M.S. students. Teaching duties include advanced biochemistry and major's biology. A biochemistry concentration is offered in both biology and chemistry (American Chemical Society accredited). Productive interactions exist among faculty in various departments on the main campus and in the Quillen College of Medicine. Applicants should submit a letter of application, curriculum vitae, statements of teaching philosophy and research interests, copies of all transcripts, and have three letters of reference sent. Electronic submission should be to: **Dr. Karl Joplin, Biochemist Search Committee, e-mail: joplin@etsu.edu.** Application review will begin on November 1, 2005, and continue until the position is filled. *Affirmative Action/Equal Opportunity Employer.*

ASSISTANT/ASSOCIATE PROFESSOR
Behavioral Neuroscience Research Faculty
Tenure Track

The Department of Psychiatry at Stony Brook University invites applicants with a Ph.D. or equivalent for a position at the level of Research Assistant/Associate Professor. Applicants should have demonstrated expertise in visuomotor, circadian, or sleep regulatory systems with use of electrophysiological recording methods. The successful candidate should be willing to collaborate with an existing laboratory studying biological rhythm regulation, the vestibular system, and nonimage forming visual system, while establishing a fully independent laboratory with his/her own research, grant support. Send curriculum vitae, statement of specific research interests, reprints or preprints of completed research, and three recommendation letters to: **Lawrence Morin, Ph.D., Department of Psychiatry, Stony Brook University, HSC T10-020, Stony Brook, NY 11794-8101**. Visit our **website: http://www.stonybrook.edu/cjo** for employment information. *Affirmative Action/Equal Opportunity Employer.*

Shriners Hospitals for Children Northern California

Postdoctoral Positions

Sacramento, CA

Postdoctoral positions are available to investigate the role of Wnt signaling during neural development using combined research approaches of mouse genetics, molecular and developmental biology. Wnts are secreted glycoproteins, which are among the most important developmental signaling molecules. Many fatal defects are observed in Wnt mutant flies, worms and mice. At least 8 Wnt signaling molecules have been implicated in human genetic diseases and colon cancer. Our recent work has revealed new roles for the canonical Wnt signaling pathway, such as in the regulation of neocortical neuronal production and organization, maintenance of hippocampal dentate granule precursor pool, and dorsal thalamic patterning. The current research projects in the lab are focused on understanding neural tube patterning, neural tube defects and craniofacial development using Wnt mutants that have already yielded exciting preliminary data. The lab is located in the recently established Institute for Pediatric Regenerative Medicine (IPRM), which occupies new, spacious, well-equipped laboratories adjacent to the MIND Institute, Cancer Center, University Hospital, and vivarium on the UC Davis Sacramento Medical Campus. Experience with transgenic/knock-out mice, histological, and molecular biological procedures is desirable but not essential.

Please send CV and letter of interest to:
Shriners Hospitals for Children (IPRM)
2425 Stockton Boulevard, Sacramento, CA 95817.
If you have further questions regarding the position,
feel free to contact: **zhoucj@itsa.ucsf.edu**. EOE

The Ohio State University University Medical Center

Post-Doctoral Positions in Bioinformatics, Medical Informatics, High-End Grid Computing, and Microscopic Imaging and Visualization

The Department of Biomedical Informatics of The Ohio State University College of Medicine in The OSU Medical Center (**http://bmi.osu.edu**) seeks applications for post-doctoral candidates with research interests in high-performance and grid computing systems, distributed databases, data-intensive computing, knowledge integration systems, knowledge management, leading-edge software infrastructure to support translational medical research, computational research programs of biomedical relevance and collaborative potential, bioinformatics, medical image analysis, computer vision, and visualization. Current research programs in BMI and affiliated departments include: high performance and data intensive computing, promoter and chromatin analysis, biomedical image processing and quantification, comparative genomics and phylogenetics, pharmacogenomics, cancer (including genetic and epigenetic variation), cardiovascular (including genetics and imaging), neuroscience, transplantation and critical care.

The successful applicant will have a Ph.D. Candidates with interdisciplinary research interests are particularly encouraged to apply. Applicants should have a publication record in leading peer-reviewed journals and demonstrated potential to obtain extramural funding.

To apply, have your curriculum vitae, a brief statement of research and teaching interests, copies of 2-4 representative publications, and 3 letters of reference sent to: Biomedical Informatics at **facultypositions@lists.bmi.ohio-state.edu**. Please state which position(s) you are applying for. The preferred format for submissions is PDF, though other formats, including hard copies, will be accepted. Hard copy submissions can be sent to the following address: **Biomedical Informatics, The Ohio State University, 3168 Graves Hall, 333 W. 10th Ave., Columbus, Ohio 43210**.

The Ohio State University is an Equal Opportunity, Affirmative Action Employer.

Faculty Positions
Gene Expression and Molecular Cell Biology
University of South Carolina

As part of the Faculty Excellence Initiative at the University of South Carolina applicants are being sought for two **Assistant Professor** tenure-track positions in the broad area of gene expression and molecular cell biology. Interests include, but are not limited to, cell signaling including Wnt pathways, post-transcriptional regulation of gene silencing, and epigenetic mechanisms controlling gene expression. Appointments will be made in participating Departments and include **Biological Sciences** of the College of Arts and Sciences and School of Medicine Departments of **Pharmacology, Physiology** and **Neuroscience,** and of **Pathology** and **Microbiology**. Future appointments are anticipated including one in the Department of Chemistry and Biochemistry to promote the expansion of these interests among current faculty in these Departments that have ongoing interactions and collaborations.

Competitive salary and startup packages will be provided. The appointed faculty members are expected to establish a successful research program and secure extramural funding. Candidates should have an interest in training graduate students, and a teaching commitment commensurate with a high quality research program is expected. Applicants with an earned doctorate, a strong research record, and postdoctoral experience should provide their curriculum vitae, a description of research plans and goals, and have three reference letters sent by **November 1, 2005** to: **Dr. Michael R. Felder, Department of Biological Sciences, University of South Carolina, Columbia, SC 29208**. Applications can be made online at **http://www.USCJobs.sc.edu**.

The University of South Carolina is an Affirmative Action, Equal Opportunity Institution.

Ludwig Institute for Cancer Research
the global cancer institute

Branch Director, Brazil

The Ludwig Institute for Cancer Research (LICR) is seeking applications for Director of its Branch in São Paulo, Brazil.

The Branch currently numbers ~150 staff and students, and is one of nine world-wide. The research focus is the understanding and control of human cancer, with an emphasis on the LICR mission of translating laboratory discoveries into clinical benefit.

The successful candidate will be a world-recognized leader in a field of research that is strongly linked to human cancer. The candidate must be willing to contribute actively to LICR's global research programs and have strong administrative and leadership skills. The Branch Director will report to the Institute's President and Scientific Directorate.

Please send a curriculum vitae, as an email attachment, to the Chairman of the Search Committee, Professor Samuel Hellman M.D., at **hrsearch@licr.org**.

LUDWIG INSTITUTE FOR CANCER RESEARCH

www.licr.org

The Ludwig Institute for Cancer Research is an Equal Opportunity Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex or national origin.

POSITIONS OPEN

POSTDOCTORAL POSITIONS:
Membrane Specialization During Epithelial Differentiation

To study the structure and function of the highly specialized mammalian bladder urothelial membrane (**website: http://www.med.nyu.edu/sun/**). Contact: **Henry T. T. Sun, Director Epithelial Biology Unit and Rudolf Baer, Professor of Dermatology, Pharmacology, and Urology, NYU Medical School, New York, NY (e-mail: sunt01@med.nyu.edu).**

The University of Hawaii at Manoa, Hawaii Institute of Marine Biology (HIMB), seeks candidates for a tenure-track **ASSISTANT/ASSOCIATE RESEARCHER** position in coastal ecosystems research. Appointment is expected to begin approximately August 1, 2006. Within this broad description, consideration will be given to candidates with expertise in the fields of sensory biology, ecological modeling, fish behavior and taxonomy, marine mammal studies, phycology, or general marine ecology. We seek outstanding candidates who have demonstrated excellence through a strong record of publication and competitive funding. Investigators whose findings hold implications that transcend the focus of a specific subdiscipline are especially encouraged to apply. A Ph.D. in biological or marine sciences is required, as are excellent communication skills and a demonstrated capability for creative, high quality research. Preference will be given to applicants with postdoctoral experience. Appointment at the Associate level will be considered in cases where the applicant has a proven record of outstanding research and grantsmanship.

Applicants should submit curriculum vitae, detailed statement of research interests, and three letters of recommendations to:

Dr. Jo-Ann Leong, Director
Hawaii Institute of Marine Biology
P.O. Box 1346
Kaneohe, HI 96744

Inquiries: **Dr. Jo-Ann Leong, Director, telephone: 808-236-7401, e-mail: joannleo@hawaii.edu.**

Review of applications will begin on December 1, 2005, and will continue until the position is filled. Applications postmarked by October 31, 2005, are assured of receiving full consideration.

HIMB is a unit of the School of Ocean and Earth Science and Technology at the University of Hawaii and is located on an island surrounded by coral reefs in Kaneohe Bay, Oahu. Please view our facilities at **website: http://www.hawaii.edu/HIMB.** *The University of Hawaii is an Equal Opportunity/Affirmative Action Institution.*

FACULTY POSITION
Molecular/Cell Biology

The Biological Sciences Department of the Florida Institute of Technology (**website: http://www.fit.edu/biology**), a premier technological university located on Florida's east coast, invites applications for a faculty position (**ASSISTANT, ASSOCIATE,** or **FULL PROFESSOR**) in the general field of molecular/cell biology starting August 2006. Candidates with interests in the basic mechanisms of cellular reproduction or cellular communication are especially encouraged to apply. Postdoctoral experience and evidence of accomplishment in research is required. Successful candidates are expected to develop an externally funded research program and participate in graduate and undergraduate teaching. Submit curriculum vitae, three letters of recommendation, and statements of research and teaching interest to: **Dr. G. N. Wells, Head, Department of Biological Sciences, Florida Institute of Technology, 150 West University Boulevard Melbourne, FL 32901. Review of applications will begin on November 30, 2005.** *Florida Tech is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.*

POSITIONS OPEN

THE UNIVERSITY OF KANSAS
Department of Chemistry

ASSISTANT PROFESSOR position in experimental physical/analytical chemistry. The Chemistry Department and the Center for Environmentally Beneficial Catalysis (CEBC), a National Science Foundation Engineering Research Center, invite applications for a tenure-track faculty assistant professor position beginning August 18, 2006. A Ph.D. in physical or analytical chemistry or closely related field, and evidence of potential to initiate a vigorous research program in experimental physical/analytical chemistry relevant to the mission of CEBC (see **website: http://www.cebc.ku.edu** for a complete description). Postdoctoral experience is desirable, as is research experience within a multidisciplinary environment (either in industry or in academia). Duties include teaching at the undergraduate and graduate levels, development and direction of a vigorous research program in an area relevant to the mission of the CEBC. Research focusing on the characterization of catalysts or catalyst support media, mechanistic investigations of new catalytic processes, or investigations of unusual fluid-phase organic reactions is of particular interest but other areas will be considered. Salary will be commensurate with qualifications and experience. Applicants should submit a letter of interest, curriculum vitae, and a summary of teaching and research interests. In addition, applicants should arrange for the submission of at least three letters of recommendation to: **Professor Brian B. Laird, CEBC Physical/Analytical Search Committee Chair, Room 2010, Malott Hall, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045. E-mail: blaird@ku.edu, telephone: 785-864-4632.** Initial review of applications will begin November 14, 2005 and will continue until the position is filled. Paid for by the University of Kansas. *Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL POSITION in insect molecular phylogenetics to study the phylogeny of Odonata and explore the evolution of flight at Rutgers University. Entomology experience is not required. We seek an interchange of ideas and expertise. We will provide analytical expertise, particularly in rRNA alignment and insect systematics. This position is supported for 18 months, starting around January 2006. Please send curriculum vitae and a letter of application that outlines the technical and/or theoretical expertise you can bring to our group to: **e-mail: kjer@aesop.rutgers.edu** by November 15, 2005. Further information about our research interests can be found at the Rutgers University websites of **Karl Kjer** and **Mike May.**

Rutgers University is an Equal Opportunity Employer.

POSTDOCTORAL POSITION
Structural Biology of Membrane Proteins

A Postdoctoral position is available in Skirball Institute, New York University School of Medicine, to determine the structures of membrane transporters and other integral transmembrane proteins using X-ray crystallography possibly in combination with cryoelectron microscopy (**website: http://saturn.med.nyu.edu/research/sb/wanglab/**). Strong background in structural biology and/or membrane protein biochemistry is required. Send curriculum vitae, statement of research interest, and names of references to: **Da-Neng Wang** at **e-mail: wang@saturn.med.nyu.edu.**

The Zoological Society of San Diego's Conservation and Research for Endangered Species (CRES) program is seeking a **POSTDOCTORAL FELLOW** to work on genetics of captive and wild gorilla populations. For more information, please visit our **website: http://www.wildanimalpark.org.**

Please submit a letter of interest, the names of three references, and curriculum vitae to: **San Diego Wild Animal Park, Attn: Human Resources #03501, 15500 San Pasqual Valley Road, Escondido, CA 92027-7017. Fax: 760-796-5614; job line information 760-738-5006.**

POSITIONS OPEN

The Mathematical Biosciences Institute (MBI) at The Ohio State University is accepting applications for **POSTDOCTORAL POSITIONS** to start September 2006, which are renewable for up to three years. Some positions are co-sponsored by industry or academic bioscience laboratories. The deadline for applications is January 18, 2006. Short- and long-term visitors may apply at any time. To access the application form or for more information, visit the MBI **website: http://mbi.osu.edu** or call 614-292-3648. *The Mathematical Biosciences Institute adheres to the Affirmative Action/Equal Opportunity Employer hiring guidelines.*

POSTDOCTORAL FELLOWSHIP
University of Lausanne, Switzerland
Molecular chaperones/protein aggregation/neurotoxic aggregation

A Postdoctoral Fellowship is available for a Protein Biophysicist and Biochemist to study the molecular mechanisms of disaggregating molecular chaperones that unfold and solubilize protein aggregates. A strong background is required in methods of protein expression and purification, recombinant DNA technology, fluorimetry, enzymology, and the ability to interact with theoretical physics. Speaking knowledge of French is recommended. Tentative start date: February 1, 2006. Send curriculum vitae, statement of goals, and names of two references to: **Pierre Goloubinoff, Ph.D., Associate Professor, DBMV, Faculty of Biology and Medicine, Dorigny campus, Lausanne University, 1015-Lausanne, Switzerland. E-mail: laurence.giddey@unil.ch.** Closing date for application: November 15, 2005.

POSTDOCTORAL FELLOW
(Stem Cell Biology)

A position is open to study the role of ubiquitylation in regulating stem cell division and differentiation. Collaborations with the stem cell core laboratory and proteomic facilities will be involved. The University of Pittsburgh provides an excellent environment for stem cell research, tissue engineering, and transplantation medicine. Candidates with strong background in ES or AS are encouraged to send curriculum vitae and three references to: **Dr. Yong Wan, Ph.D., University of Pittsburgh, Hillman Cancer Center, 5117 Centre Avenue, Room 2.6C, Pittsburgh, PA 15213. E-mail: yow4@pitt.edu.** *An Equal Opportunity/Affirmative Action Employer.*

ANNOUNCEMENT

ALASKA'S NORTH SLOPE SCIENCE INITIATIVE SEEKS TECHNICAL GROUP NOMINEES

Alaska's North Slope Science Initiative (NSSI) is seeking nominees for a Science Technical Group (STG). The STG provides advice to principal regional, state, and federal government agencies with management responsibilities for public lands, fish, and wildlife across the North Slope of Alaska. Nominations to the STG may be received from individuals that have proven records in science and resource management on the North Slope of Alaska. For more information or to request a nomination packet call: **Ken Taylor, Executive Director, NSSI, at telephone: 908-271-3131,** or visit our **website: http://www.northslope.org.** Deadline is October 27, 2005.

Find out about jobs before you get your issue. Sign up for customized e-mail notification of jobs at **website: http://www.sciencecareers.org** by clicking on Job Alerts. You can also post your resume (open or confidentially) and check how many employers have viewed your resume at your own convenience.

ASSISTANT/ASSOCIATE/PROFESSOR
within
The Department of Biomedical Engineering
The University of Michigan

Building on recent initiatives in cellular and molecular biotechnologies, the BME Department at the University of Michigan is soliciting applications for new faculty positions. We are especially interested in candidates working in the general areas of biomaterials and cellular engineering for applications in cardiovascular and neural systems. The successful applicants for these positions will help link these areas to existing research strengths in the department and CoE. Qualifications include an earned Ph.D. in an engineering or natural science discipline related to biomedical engineering, and demonstrated excellence in, and commitment to, teaching, research, and scholarship. Women and minority candidates are encouraged to apply.

Applicants should send a letter of interest with curriculum vitae and a list of references to:

Biomedical Engineering Search Committee
Department of Biomedical Engineering
The University of Michigan
1107 Carl A. Gerstacker Building
2200 Bonisteel Boulevard
Ann Arbor, MI 48109-2099

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Advertisement for Neuroscience Positions

The Program in Neuroscience at the Florida State University seeks to fill six new tenured or tenure-track faculty positions over the next two years as part of a major university initiative to expand neuroscience research across campus. The initiative includes the development of a major basic science quadrangle, already home of the newly established College of Medicine, and the construction of two new research buildings for the Departments of Biological Science and Psychology. When completed, these three projects will collectively add about 490,000 gross square feet of new space and 120 new research laboratories dedicated to biomedical and behavioral research.

The Program in Neuroscience (**http://www.neuro.fsu.edu**) is a highly interactive and interdisciplinary program that encompasses 25 faculty members in 8 departments. Current research strengths include motivated behaviors, sensory systems, biological rhythms, learning and plasticity, development, ingestion and metabolism, neuroendocrinology, and computational neuroscience. We seek applications from noted scholars with a track-record of productivity and independent support who will enhance our current strengths or expand the program in novel directions. We invite applications for faculty positions at the rank of assistant, associate, and full professor. Appointments will be in relevant departments. Senior investigators are encouraged to contact Rob Contreras, the Program Director, (**contreras@neuro.fsu.edu**) to discuss the possibility of multiple hires to form a specific research cluster.

Review of applications will begin on **1 December 2005**, but the search process will remain active until the positions are filled. Please send a cover letter, curriculum vitae, representative papers, a 2 to 4 page research plan, and the names and contact information of 3 references. Application materials can be sent electronically to **search@neuro.fsu.edu**, or by mail to: **Janice Parker, Administrator, Program in Neuroscience, Room 18, LON-1280, Florida State University, Tallahassee FL 32306-1280, Phone: (850) 644-3076, FAX: (850) 644-0349.**

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Faculty Positions in Host-Pathogen Interactions
The Ohio State University
Department of Microbiology and Center for Microbial Interface Biology

The Department of Microbiology and the Center for Microbial Interface Biology (CMIB) at The Ohio State University invite applications for two tenure-track faculty positions at the Assistant Professor level. The successful candidates will have a PhD or/and MD/DVM, postdoctoral experience, documented evidence of high quality research, and a commitment to teaching and research at a major research university. They will be expected to establish independent research programs focused on microbial pathogenesis, or the host response to a microbial pathogen, supported by extramural funds and will have opportunities for cooperative research with colleagues engaged in other aspects of microbe-host interactions. They will participate in teaching undergraduate and graduate students. Expansion, by recruiting additional faculty in these areas will continue over the next several years. The individuals hired will have joint faculty appointments in the Department of Microbiology in the College of Biological Sciences and in the CMIB in the College of Medicine. The goal of the CMIB is to focus multidisciplinary research on the complex relationships between microbes and hosts, including pathogens related to biodefense. Very competitive salaries, start-up packages, and excellent biosafety level III, DNA, RNA and protein core facilities are available.

Applicants should submit a letter of interest, C.V., description of research plans and the names of at least three potential referees electronically to **microsearch@osu.edu** (preferred) or by mail to: **Search Committee Chair, Department of Microbiology, 484 W. 12th Ave., Ohio State University, Columbus OH 43210-1292**. Additional information describing the Department of Microbiology and CMIB can be found at **http://www.osumicrobiology.org/** and **http://cmib.osu.edu**. To ensure full consideration, applications should be received by **December 1, 2005**, but applications will be accepted until the position is filled.

To build a diverse workforce Ohio State University encourages applications from individuals with disabilities, minorities, veterans, and women. Flexible work options are available. EEO/AA Employer.

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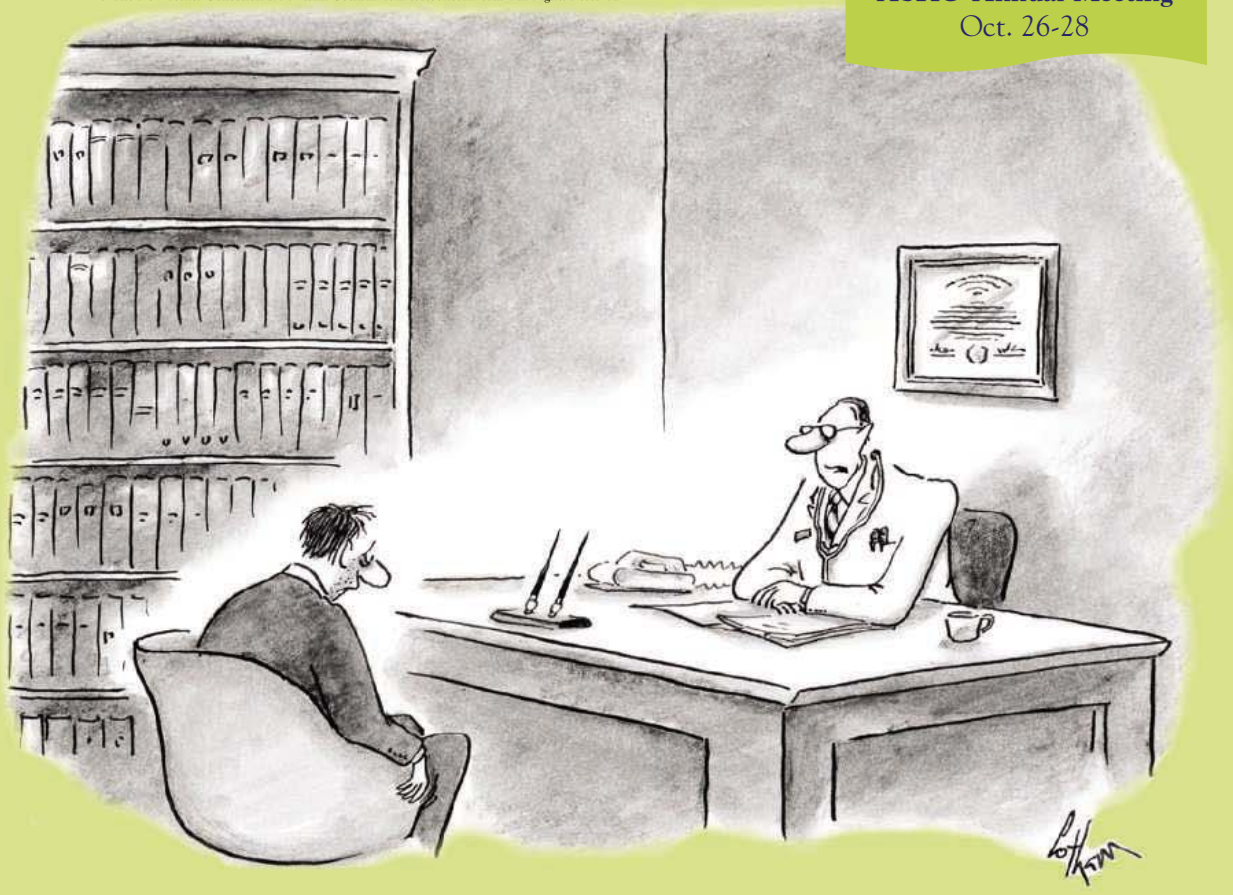

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